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THE ANNALS OF THORACIC SURGERY

olume 30 Number 1 July 1980

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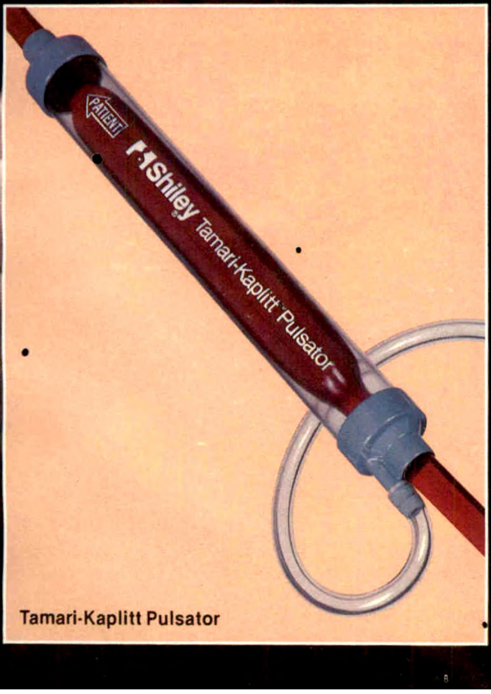

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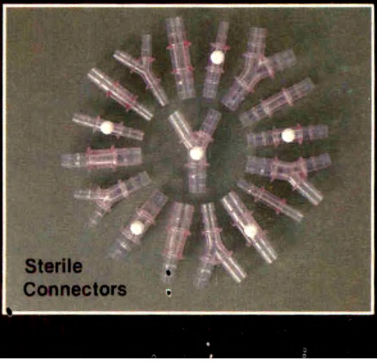

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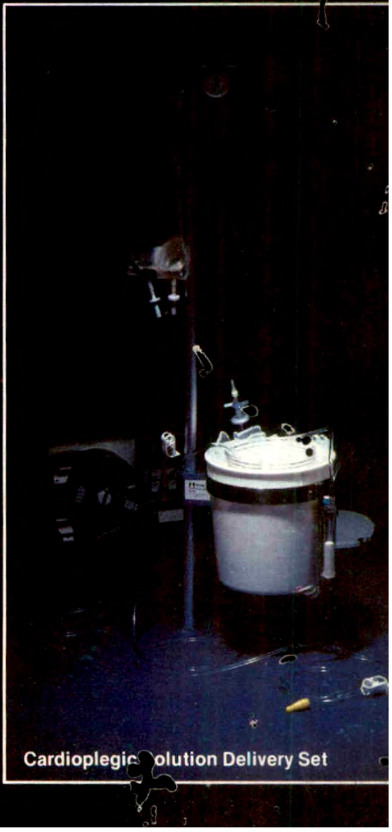

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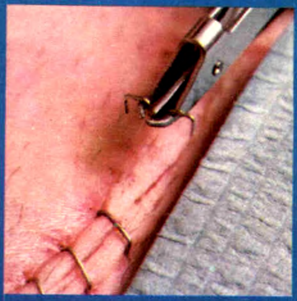

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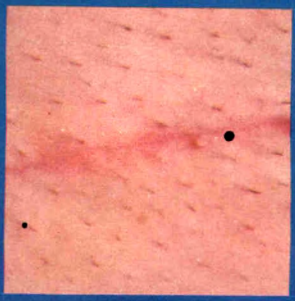
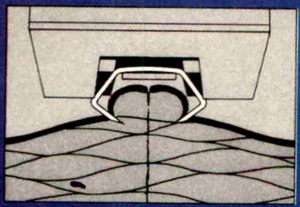
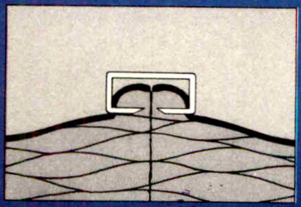




Touch skin lightly using centerline indicator and guide notch to ensure equidistant staple placement across the inc[illegible]on. Fire, release complet[illegible]nd withdraw instrument with backward motion.



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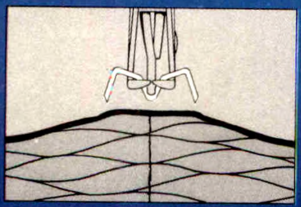

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THE ANNALS OF THORACIC SURGERY

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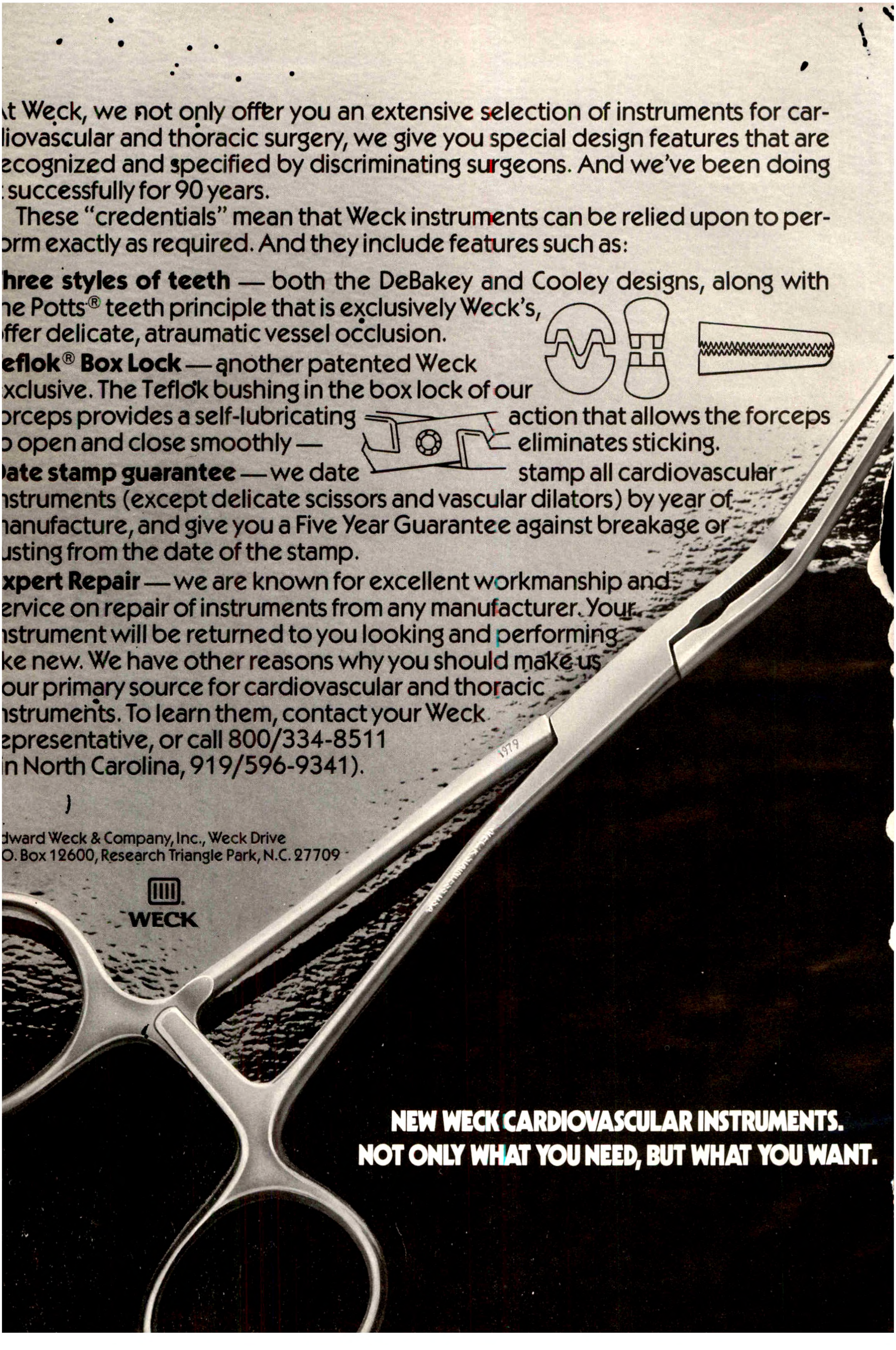

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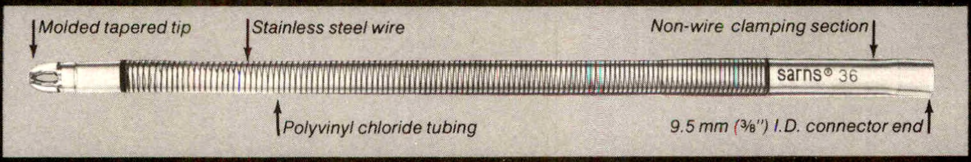
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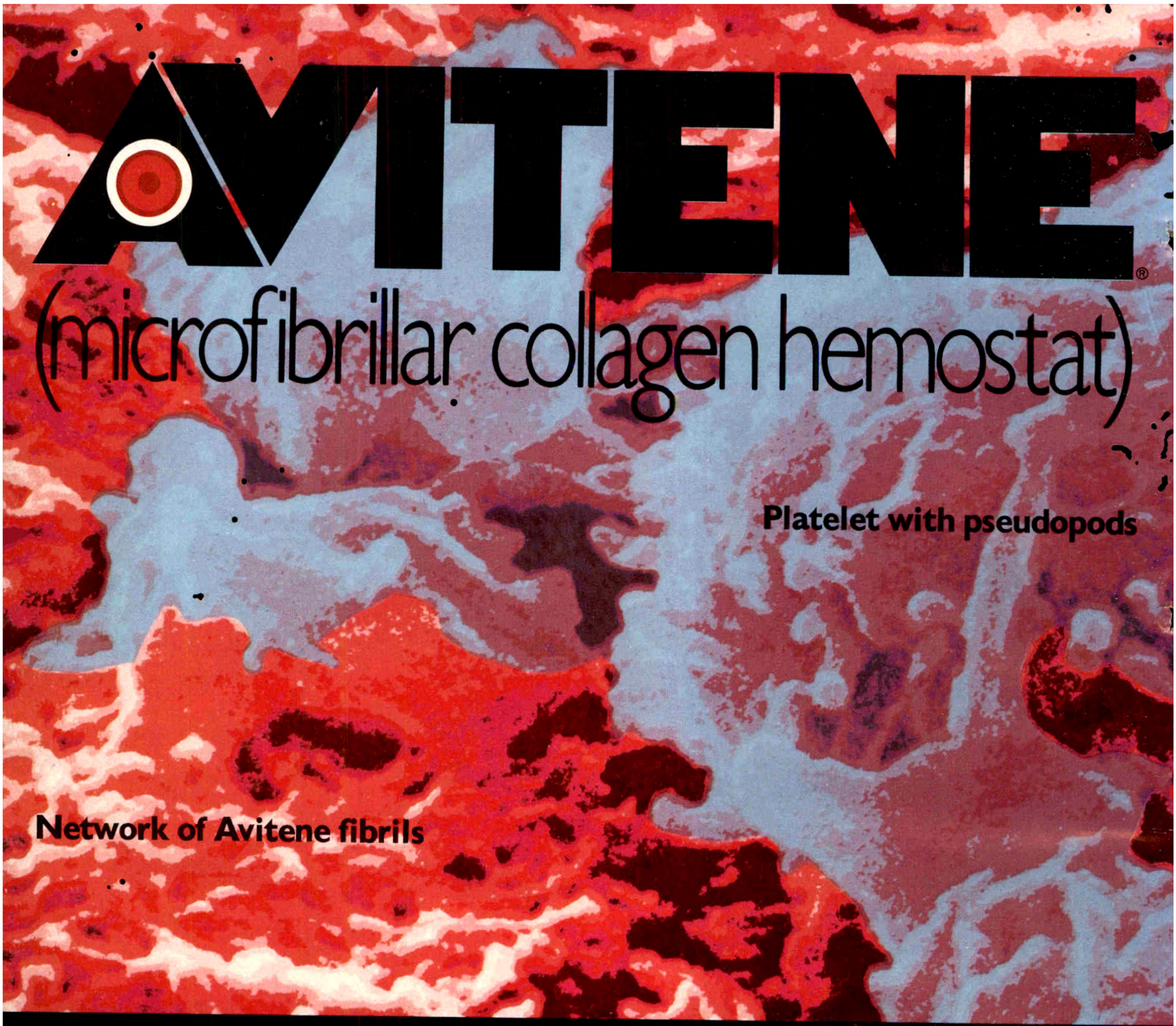

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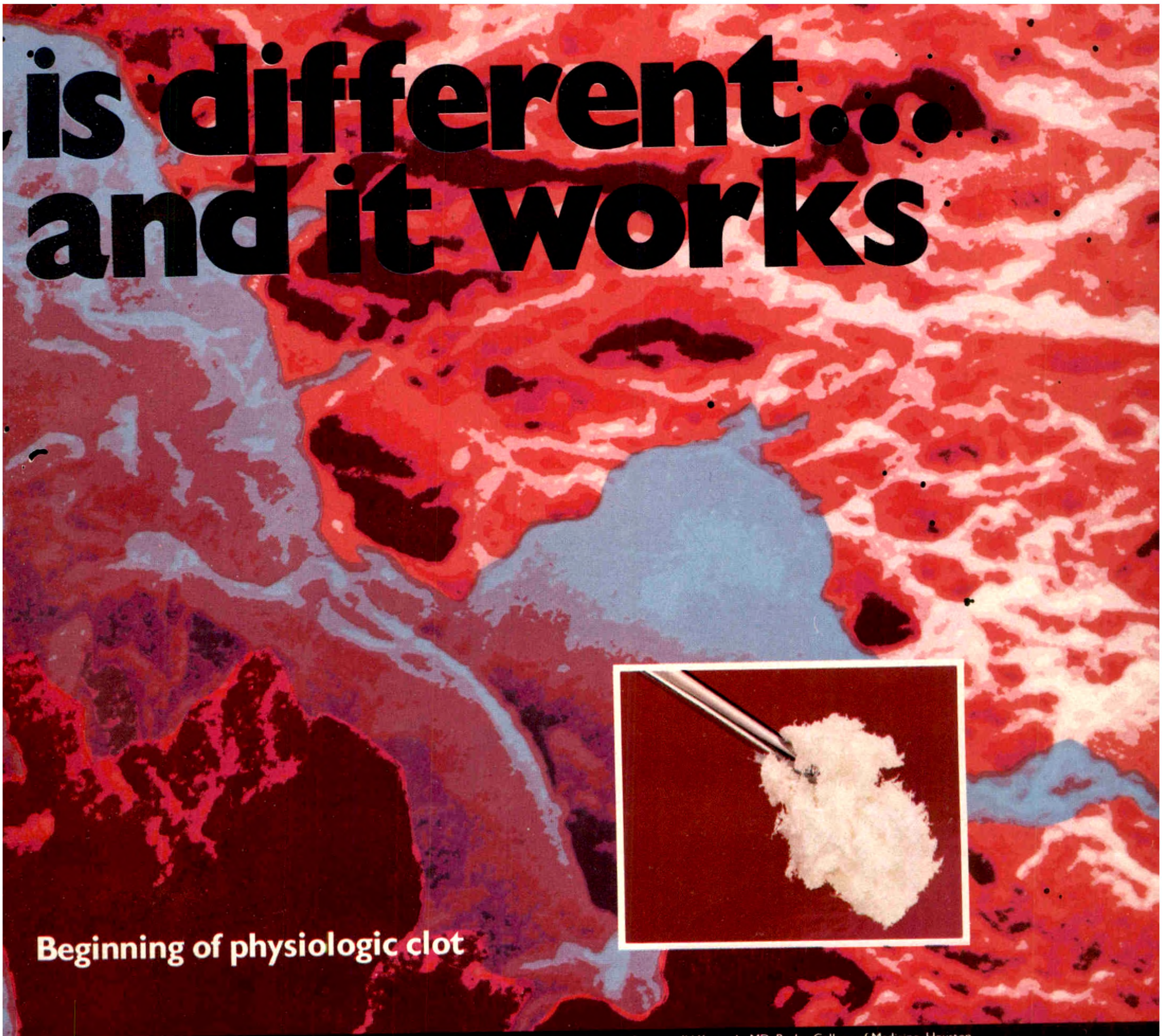

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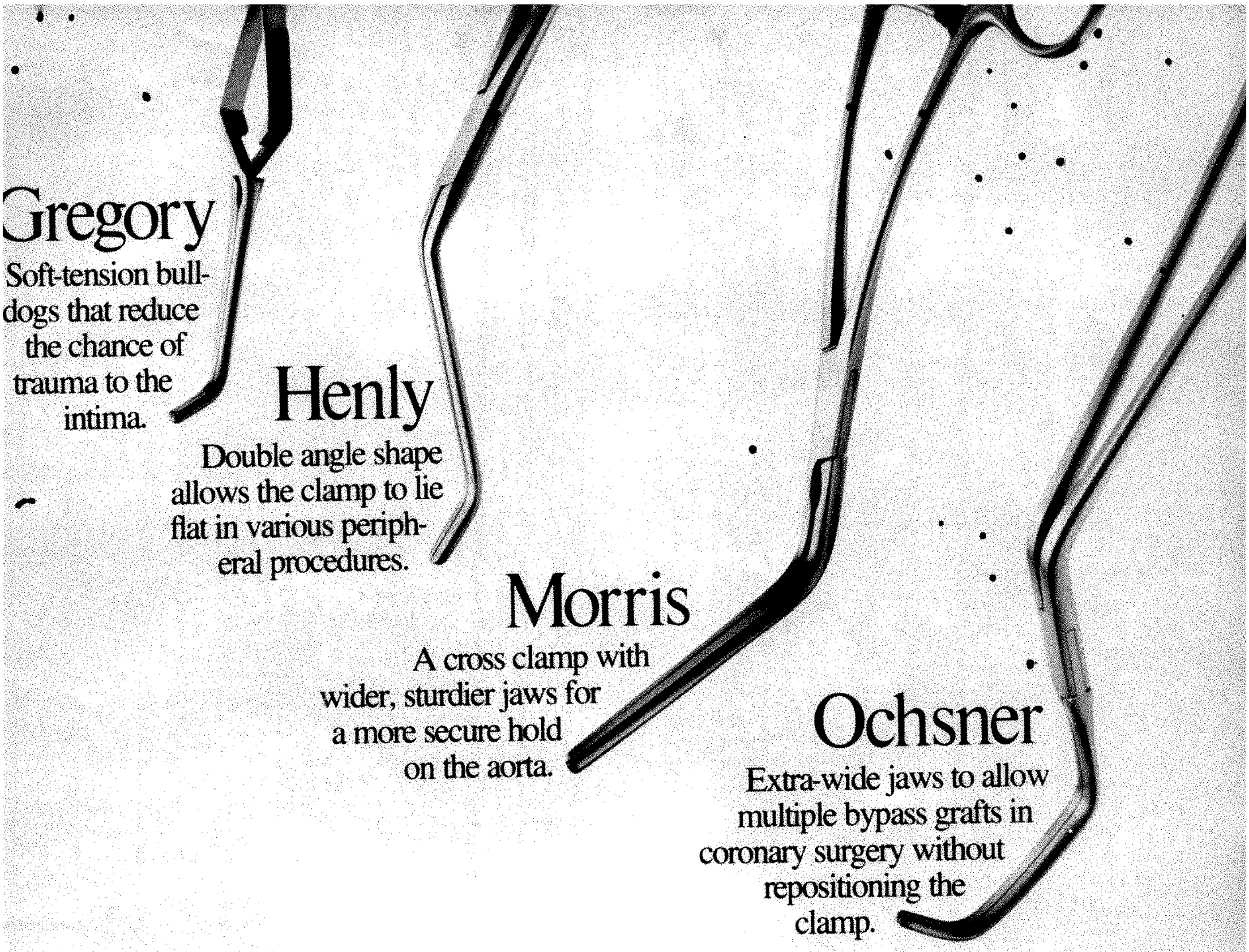

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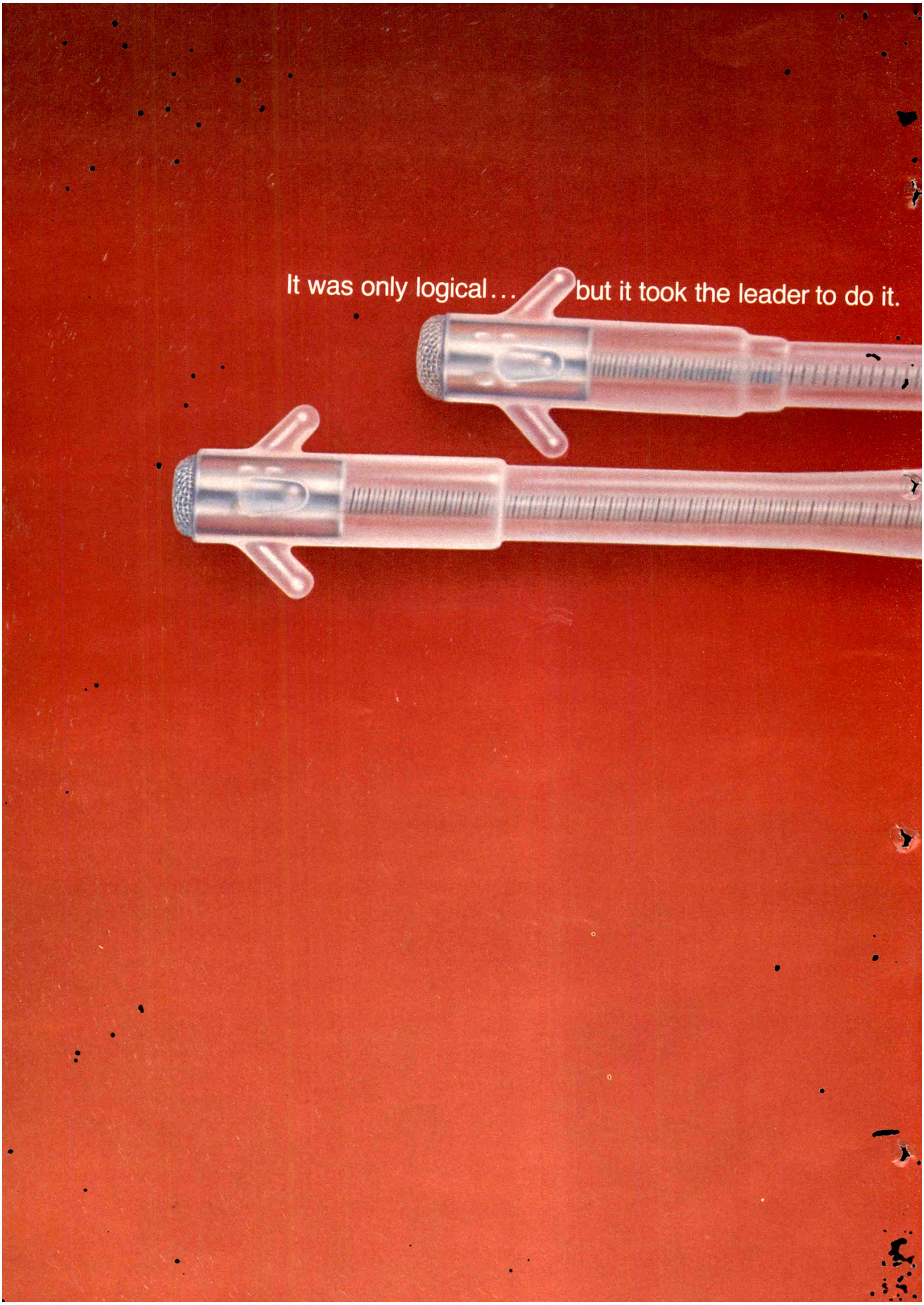
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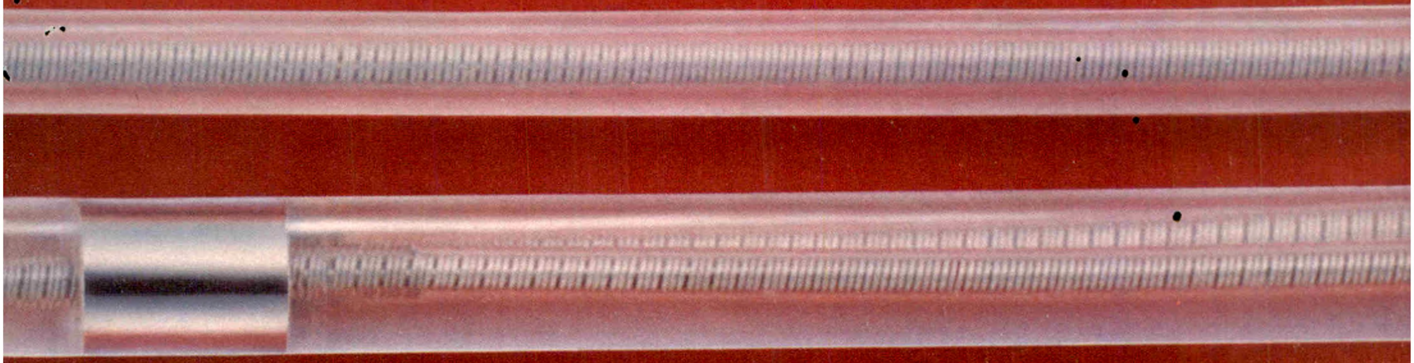

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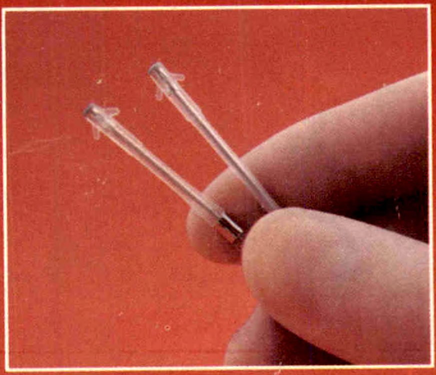

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EDITORIAL

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8.1.8

What Is the Role of Intraoperative Manometry?

Tom R. DeMeester, M.D.

The understanding that symptomatology of hiatus hernia was linked with the occurrence of gastroesophageal reflux directed surgeons' attention to improving the lower esophageal sphincter rather than simply reducing the hernia by closure of the crura. The Allison repair represented the first efforts in this direction and emphasized the need to replace the gastroesophageal junction into its normal intraabdominal position in an effort to improve its function [1]. Recognition of the high incidence of symptomatic and anatomical recurrence after the Allison repair [2] led to the development of procedures designed to place and anchor the lower esophagus in the intraabdominal position in a more effective manner. A posterior gastropexy, which anchors the phrenoesophageal membrane and thus the cardioesophageal junction to the median arcuate ligament of the aortic hiatus, was introduced by Dr. Lucius Hill of Seattle [7]. Two other operations, the Belsey Mark IV [11] and the Nissen fundoplication [10], introduced the concept of using a cuff of stomach as a means of establishing and anchoring an intraabdominal segment of esophagus. An unrecognized benefit of the gastric fundic wrap used in the Belsey and Nissen procedure was augmentation of the lower esophageal sphincter pressure. This did not occur to the same degree when the Hill procedure was done as described in its early form [4].

Awareness of the increasing importance of the distal esophageal sphincter pressure as one of the components of the antireflux mechanism and the observation that his operation did not augment sphincter pressure as well as the gastric fundoplication operations stimulated Hill to modify his operative technique. This resulted in his introduction of intraoperative measurement of the lower esophageal sphincter pressure [8]. He encouraged the use of intraoperative manometrics as a simple and safe technique to quantitate improvement in the sphincter pressure and recommended that an imbricating suture to calibrate the cardia be added to his previously published surgical technique. This suture is tied while sphincter pressure is measured. A sphincter pressure between 45 and 57 mm Hg is desirable since on clinical experience this gives a proper balance between the correction of gastroesophageal reflux on the one hand and the creation of dysphagia on the other. Hill [8] stated that calibration of the sphincter should be routine for operations designed to correct gastroesophageal reflux.

Hill's zeal influenced Dr. Joel Cooper from Toronto to report his unit's observations on intraoperative esophageal manometry with the Collis gastroplasty and Belsey hiatal hernia repair for gastroesophageal reflux [3]. Cooper and co-workers advocated the use of intraoperative manometrics, although not as enthusiastically as Hill. Dissatisfaction with the statistics supporting the use of intraoperative manometrics presented in the articles of Hill [8] and Cooper and colleagues [3] moved Dr. Orringer and colleagues at Ann Arbor to report their findings in this issue of The Annals (p 13).

An evaluation of the proper role of intraoperative manometrics based on these three reports might well begin by enumerating the observations common to them all since assent of three groups to the same observation is more apt to be a reliable indicator as to how things really are. Having established a common ground, it might then be easier to reconcile the differences.

The first common observation is the lack of difference in the distal esophageal sphincter pressure measured before and after the induction of anesthesia. This is somewhat surprising since anesthesia does reduce the tone of anatomically recognizable sphincters. This would support the concept that the distal esophageal high-pressure zone is not due to the function of

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a distinct muscle bundle but more likely to the geometry of the smooth muscle at the cardia [9]. As such, its baseline tone is maintained even under anesthesia.

The second common observation is that the sphincter pressure recorded in situ did not differ from that recorded when the sphincter was exposed to atmospheric pressure. Cooper, Orringer, and their co-workers failed to observe a difference in sphincter pressure with the chest closed or opened, which indicates that sphincter pressure is not greatly affected by the negative intrathoracic pressure. Similarly, Hill failed to observe a difference in the sphincter pressure with the abdominal cavity closed or opened, indicating that the positive intraabdominal pressure has minimal effect on the sphincter pressure. This would seem reasonable in that the intragastric pressure used as a baseline to measure the height of the sphincter pressure would be affected similarly by opening the abdomen. A more precise evaluation of the environmental effects on sphincter pressure would be to use atmospheric pressure rather than the gastric pressure as a reference point.

The third common observation is that both the construction of a gastric fundoplication as described by Belsey and Nissen and imbrication of the cardia as described by Hill increase the sphincter pressure. This indicates that surgical reconstruction of the cardia is able to increase sphincter pressure and that this improvement is greater than that reported with any form of medical therapy.

The fourth common observation is that measured postoperative sphincter pressures were one-half the intraoperative values measured after repair. Cooper, Orringer, and their colleagues commented that the increased pressure in the sphincter and in the constructed gastroplasty tube measured intraoperatively was associated with spasm of the distal esophagus and gastroplasty tube. Further, Orringer and associates showed that simple operative mobilization of the cardia increased sphincter pressure over that observed preoperatively and after the induction of anesthesia. This would indicate that manipulation of the esophagus, like all other smooth muscle organs, causes a certain amount of spasm, which is responsible for the high pressure recorded during operation. This spasm is probably due to trauma or partial ischemia secondary to the surgical dissection. Temporary elevation of sphincter pressure secondary to spasm should be appreciated by all who depend on intraoperative manometry as a guide in surgical reconstruction of the cardia, a point Hill has emphasized repeatedly.

The fifth common observation is that the increase in sphincter pressure obtained following surgical repair of the cardia remained stable up to twelve months in 21 of Orringer's patients and 6 of Cooper's patients, and up to thirty-six months in some (unspecified) of Hill's 200 patients. It is encouraging to note that augmentation of sphincter pressure, one of the known components of the antireflux mechanism, by a surgical reconstruction of the cardia remains stable. In my own experience with 4 patients, it has remained stable up to five years.

The three papers differ as to whether the use of intraoperative manometry is necessary in order to do an adequate antireflux operation. Hill [8] stated that it is in order to obtain control of reflux without producing dysphagia. He strongly believes that there is an individual correlation between the measured intraoperative and the subsequent postoperative sphincter pressure, although he does not give data to support this.

Cooper [3] admits that data obtained by him and his colleagues do not allow him to state categorically that intraoperative pressure measurements are in any way related to the subsequent postoperative measurement in the individual patient. He believes that the number of patients his unit studied were too few and the length of clinical follow-up too brief to permit any meaningful conclusion in this regard. He considers it possible that if a larger number of patients was studied for a longer period of time, a correlation might occur between the intraoperative pressure measurement and the subsequent clinical course of the patient. If this is true, it would support doing intraoperative manometrics routinely and would indicate the necessity of redoing a procedure if an inadequate pressure was measured at completion of the repair, a thought not relished by many surgeons. He believes, however, that the Collis-Belsey repair has yielded such good clinical results at the present time that a need does not exist to modify the intraoperative repair, regardless of the pressure measured.

Orringer and associates, on the other hand, state categorically that if the intraoperative and subsequent postoperative distal esophageal sphincter pressures obtained in individuals are compared, no statistical correlation is found between what was measured intraoperatively and the subsequent pressure postoperatively. They claim that this applies not only to their data, but also to the data that they were able to evaluate from the report of Cooper and coworkers [3]. They conclude that intraoperative manometry cannot be relied upon to predict the future success of an antireflux operation. Since it adds a minimum of 30 to 45 minutes to the operation and since the information gained is of little practical value or statistical significance, it should not become a necessary component of the procedure.

The position of Orringer and associates is supported by clinical studies in nonsurgical patients in whom it has become evident that the magnitude of the sphincter pressure is not related to the competency of the cardia in the individual patient. Some individuals with low pressure have a competent cardia, whereas others with high pressure have an incompetent cardia [5]. On the other hand, the main support for sphincter pressure as an important factor in competency of the cardia rests on population studies in which the *mean* pressure recorded in a group of patients with reflux is lower than that measured in a group of controls or in the same patients after surgical repair [4, 6]. These findings when analyzed indicate that sphincter pressure is not the only factor on which competency of the cardia depends. As mentioned before, the length of the abdominal esophagus is also important [5]. No doubt, as more of the physiology of the cardia becomes elucidated, other factors that contribute to competency will be uncovered. Faced with this current state of knowledge, it would be unwise for a surgeon to place all his attention and effort on increasing the distal esophageal sphincter pressure when performing an antireflux procedure, as important as it might seem at the moment.

In summary, intraoperative measurements of distal esophageal sphincter pressure have been of more value in providing information about the physiology of the cardia than in serving as a necessary tool for performing an adequate antireflux procedure. The inadvertent benefit of augmenting the distal esophageal sphincter pressure with a partial or complete fundoplication obviated the necessity to improve this component of the antireflux mechanism when performing the Nissen or Belsey repair. The use of the surgical imbrication stitch to increase sphincter pressure in the Hill repair accomplished what the fundoplication does in both the Nissen and the Belsey procedures. Indeed, Hill's own experience indicates that the nature of his operation makes it mandatory to perform intraoperative manometrics in order to obtain a successful repair. The failure of Orringer and co-workers to find any correlation between intraoperative and subsequent postoperative sphincter pressure measurements when using a fundoplication procedure places the necessity on Hill to present data indicating that his intraoperative pressure measurements correlate with those he obtains postoperatively. It may be that imbrication of the esophagus as done in the Hill repair would allow for such a correlation. It appears, however, that those surgeons using the Hill procedure should depend on intraoperative manometrics to provide them with objective evidence that they have augmented one of the important determinants of the antireflux mechanism. This does not seem to be necessary when performing the Nissen or Belsey procedure.

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Accentuating the Positive

Paul C. Adkins, M.D.

ABSTRACT **The Society of Thoracic Surgeons is the largest organization representing our specialty. At this time, escalating costs of medical care and the public demand for accountability have given rise to a number of issues that must be faced. The Society is in a position to lead the medical profession in addressing many of these issues. We must present a united front for our specialty and resolve problems involving our training programs, manpower, federal regulations regarding medical devices, and the Federal Trade Commission's position on advertising. Additionally, the organization must address the issue of a definition of physician competence as it relates to the certifying and recertifying process. Awareness of these problems by all members of the Society with the opportunity for open discussion is essential. It is vital that The Society of Thoracic Surgeons assume a visible positive position on these issues.**

The Society of Thoracic Surgeons is the largest organization in the world representing our specialty today. We have 1,812 active and 109 senior members. In the 1979 edition of the *Directory of Medical Specialists* [5], there were 3,331 Board-certified thoracic surgeons listed for the United States and Canada. Although no one knows the exact figure, approximately 2,500 of these individuals are currently active in the practice of thoracic surgery. Thus, our organization represents the vast majority of practicing thoracic surgeons in the United States. It serves uniquely as a forum for all elements of our specialty from the full-time academician to the private practitioner. In its 16-year existence, this society has matured under the direction and leadership of the giants of our field, many of whom are present today. It has produced numerous innovative ideas and concepts in its scientific programs and other educational activities.

Yet as we enter the last two decades of the twentieth century, we are met with challenges that did not exist 16 years ago when this organization was founded. The issues being thrust upon us are not unique to our specialty of thoracic surgery nor to the medical profession alone, but are a reflection of what is transpiring in the entire world. They represent part of a worldwide shift in forces and link economic, social, political, and ethnic concepts, and have an impact on those basic philosophical principles that traditionally have directed Western civilization. In his superb Presidential Address last year, Harold Liddle outlined the background and developments leading up to the present position of the medical profession. In effect, beginning in the early 1950s, the American public was promised its right to medical care. The advent of Medicare and Medicaid led to further federal involvement at all levels, even to that very personal relationship between doctor and patient. Even these last terms in the eye of the economist are becoming obsolete. Patients are no longer patients; they are consumers. We are the providers, and we are no longer a profession, but the health care industry. With health care now representing more than 9% of the gross national product, at a level of $200 billion a year, the federal government and indeed now the third party carriers are functioning in a variety of ways to attempt to control these escalating costs.

Kaplan's Law and Medicine

While we all realize that cost is probably the major problem facing the medical profession today and have taken some voluntary steps in an effort to control this, the many and various federal activities in this area have led to a phenomenon which Ronald Kaufman [9] identified as Kaplan's law. Abraham Kaplan was a professor of physiology at the University

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of Michigan and quite interested in science and technology. His law of the instrument is that if you give a small boy a hammer, suddenly everything he encounters needs pounding. Thus, the federal government in its numerous branches has become involved, not only in cost-effectiveness, but in manpower, medical education, allied health, health care technology, and almost all other activities related to this field. As regulations escalate, personal freedom diminishes, and the federal involvement in these areas has resulted in a serious infringement upon our freedom as physicians and surgeons to make decisions regarding patient management. No longer will there be a question of "can we do it" but rather "should we do it?"

As you know, this process occurred with end stage renal disease and its management both in this country and in England, fortunately with somewhat different results as far as the United States was concerned. Soon operations for coronary artery disease may be subject to economic scrutiny by the newly founded quasi-federal instrument, the National Council on Health Care Technology. Although in the beginning this council proposes to look at the type of institution where coronary artery operations are performed, it seems almost inevitable that sooner or later the cost-effectiveness of this procedure in terms of future employability and productivity of the patient or consumer, if you wish, will be analyzed. We will then be faced with questions or judgments of not whether the patient should have the operation, but what the impact of such a procedure will be on the economy.

As you are well aware, the medical profession is being castigated almost daily in the media: unnecessary operations, second opinions, cost containment, cost-effectiveness, and public accountability are words or phrases spoken so frequently that they have become almost synonymous with the perception of the public that the medical profession cannot cope. In the words of Steven Potter [12], "if you are not one up, you are one down," and at this point in the public eye, the medical profession is, by and large, one down.

Perhaps one reason that we find ourselves in this position is the lack of a united front. A prime example of this lack of unity is the American Medical Association's recent withdrawal of support for the Liaison Committee on Continuing Medical Education. There are approximately 400,000 practicing physicians in the United States: it is a large force, yet with a wide spectrum of interests, allegiances, politics, and attitudes—scarcely a unified group. In general, the profession has been identified as having a negative attitude toward many of the issues. We see the growing federal encroachment as a threat to our freedom as physicians and have objected, but rarely have we offered viable options. It is my belief that the specialty of thoracic surgery, as represented by this organization, is in a position to be a leader in facing the issues confronting the entire profession. In a recent article by Bloom and associates [2]—presumably unbiased observers since none are surgeons—the work characteristics of thoracic surgeons were studied by random sample. The authors conclude that "thoracic surgery represents a prototype of what a surgical specialty should be. Thoracic surgeons are unusually well trained and they work longer hours than other specialties in this country." We have accounted for more innovations and advances in the past several decades than almost any other medical specialty. The qualities of leadership are here.

Issues in the Society

Division of the Specialty

In order to assume the mantle of leadership, we must define as much as possible the problems facing us in the coming years. Initially we must decide what we are and what we represent. Are we cardiac surgeons, general thoracic surgeons, vascular surgeons, or a combination of these? Many would answer that we are all three, but there are forces without and even within our profession who would like to see us splintered. We hear "I am a cardiac surgeon; give esophageal and pulmonary operations back to the general surgeons." There are those who believe that vascular surgery is a specialty of its own. But look at the emblem of The Society of Thoracic Surgeons: it encompasses all areas that I have mentioned. Particularly, I direct your attention to the lower left quadrant of the seal where we are unmistakably identified as being involved in vascular surgery. Indeed, based on the recent manpower survey, 43% of the respondents indicated that 20% or more of their practice is vascular surgery [1]. This involvement was confirmed by the responses to the annual meeting questionnaire. The Society of Thoracic Surgeons should take a firm stand on its involvement in this area, considering that an impasse now exists between the American Board of Surgery and the American Board of Thoracic Surgery regarding vascular training. Consideration should be given to including vascular surgery papers on future programs.

Let us not forget our heritage. Thoracic surgery as a specialty was an offshoot of general surgery under the guidance of our illustrious forebears, Alexander, Graham, Churchill, and Blalock. We have resisted the trends of some other surgical specialties to minimize the residency years before specializing. We have the only primary certifying Board in which certification in general surgery is a prerequisite for eligibility. I believe it is because of this broad background that many of the innovations and concepts of our specialty have come into being. Attempts to alter the training period have failed. An example is the "three and three programs" with elimination of certification by the American Board of Surgery, as tried during the past decade. While from a practical standpoint in our day-to-day activities, most of us are identified as cardiac surgeons or general thoracic surgeons, let us not alter the broad base of our training.

The entire issue of division of the specialty was addressed by the Society of Thoracic and Cardiovascular Surgeons of Britain as outlined by J. Leigh Collis in his Tudor Edwards lecture [4]. It was pointed out that that society had voted three times on the issue of dividing into cardiac surgery on one hand and pulmonary and esophageal surgery on the other as separate specialties. At each vote, in 1965, 1974, and 1978, the concept was rejected in favor of unity of the specialty. In the United States for many years, there has been a division of our specialty within the structure of the American College of Surgeons. There has been the Cardiovascular Committee, which is basically in charge of the cardiovascular portion of the scientific program for the annual Congress of the College. On the other hand, a totally separate group, the Advisory Council for Thoracic Surgery, has had as its responsibility the general thoracic portion of the program. Recently, the regents of the College have stated that the Advisory Committee for each specialty will have direct annual access to the Board of Regents as a spokesman for that specialty. In recent months, Dr. Herbert Sloan, President of the American Association for Thoracic Surgery, and I, representing the Society of Thoracic Surgeons, with the concurrence of the respective Councils, have written to the Board of Regents requesting that the Council be renamed and redefined as the Advisory Council for Thoracic and Cardiovascular Surgery. We have reason to be optimistic that this request will be approved.

Residency Training Problems

I would like to address another issue regarding our training, and that is the problem of the volume of congenital heart operations. Ask any program director in thoracic surgery today what the greatest problem is in residency training, and two out of three most likely will answer "finding sufficient congenital heart operations for the residents." One of the frequent problems encountered by the Credentials Committee of the American Board of Thoracic Surgery in reviewing individual operative experience of the candidates is also the volume of congenital heart operations. In the majority of training programs today, it is difficult, if not impossible, to train residents in a 2-year period to do all procedures from mediastinoscopy to complex congenital heart operations.

Is there a need to train 120 residents per year to operate on complex congenital anomalies such as transposition of the great vessels? Obviously, the answer is no. A review of the operative experience of those candidates applying for certification by the American Board of Thoracic Surgery in 1979 revealed that the mean number of congenital heart operations done by the candidates was twenty-six, of which fourteen were open-heart operations, the majority of them simple defects. This is hardly a wide experience, and most surgeons entering the field of congenital heart surgery have perceived the need for additional training in this area. Program directors and the current and future directors of the American Board of Thoracic Surgery are going to have to face this issue squarely. It seems to me that it is time to acknowledge that there is a limited need for thorough training in complex congenital heart operations. Perhaps a small number of programs, ten or twelve, could offer additional training in neonatal cardiac operations and the treatment of complex congenital heart defects. For those few programs that are rich in case volume in this area, the additional time would not be necessary. Whether or not formal subcertification in this field would be forthcoming is not pertinent at this point. I do not propose to eliminate congenital heart surgery from training programs, but simply to recognize the limited material and limited need to train residents in this highly specialized field. Acknowledging this should make life easier for program directors and in no way diminish the dedication to excellence in other areas of our training programs.

Manpower

Another issue which we must address is that of manpower or "surgipower," if you wish. As you are aware, there are currently many groups scrutinizing the problem of present supply and distribution of physicians in all specialties and attempting to make projections for the future. A variety of federal agencies, including the Health Resources Administration and the Bureau of Health Manpower of the Department of Health, Education, and Welfare, the Federal Trade Commission, and the Government Accounting Office, are involved. Up to now, most of this federal involvement has concerned itself with the availability of primary care physicians, particularly in the disadvantaged, low population areas and in the inner city. However, as some form of national health insurance program draws closer, it seems apparent that there will be more federal concern with the supply and distribution of specialty physicians under the guise of controlling cost.

Currently, another group under the sponsorship of the Department of Health, Education, and Welfare, the Graduate Medical Education National Advisory Committee (GMENAC) is working to develop specialty manpower projections for 1990. The methodology used by GMENAC in its Delphi Advisory Panels representing the various specialties is of some interest. Its projections are based on an estimate of the incidence of various disease entities per 100,000 population that might be encountered in the year 1990. From this, the number of hours that a thoracic surgeon, for instance, might devote to each entity in that year is derived. Then, estimating the average work week for a thoracic surgeon and the average number of hours devoted to the various disease entities that he or she would be likely to encounter, one can derive a formula for estimating the number of full-time equivalents in thoracic surgery needed for that year. As might be imagined, there are a number of very subjective aspects to this form of calculation and a 10% increase or decrease in the number of hours in a work week would have a substantial impact on the manpower requirements.

In our own organization, the Ad Hoc Committee on Manpower presented a summary of its findings based upon a survey for 1976 in a recent issue of *The Annals of Thoracic Surgery* [1]. This survey, covering the activities of 2,240 active thoracic surgeons in the United States, indicates that we are not shorthanded. Although, as Dr. Ferguson [7] noted, averages mean nothing for individuals, the average case load of major thoracic and cardiac operations was less than two cases per week per surgeon. Obviously, this does not include minor procedures and peripheral vascular operations. At the same time, the majority of respondents indicated that they could handle an additional two cases per week, double the current volume, with their current staffing and facilities.

In the same issue of *The Annals*, a projection of future manpower needs by Dr. Paul Feldstein and Hilary Viets [6] was published as an accompanying paper. Their projection included the options of certifying 160, 120, and 80 thoracic surgeons per year over the next 30 years. They also projected linear increases in the frequency of the various diseases that thoracic surgeons are liable to encounter over the next several decades. I have some problem with the last item in that from what can be derived from the available data, the number of operative procedures for lung cancer, esophageal disease, and congenital heart disease do not appear to have increased substantially over the past 5 years. The single major change in our speciality is the escalation in frequency of operations for coronary artery disease. Consequently, other than in the field of coronary artery bypass operation, one might project that the frequency of other procedures will be related basically to the increase in population. Based on the National Thoracic Manpower Survey of 1970 by Dr. Lyman Brewer and others [3], and The Society of Thoracic Surgeons Manpower Survey of 1976 [1], the apparent need is 1 thoracic surgeon per 100,000 population. According to the Census Bureau, the population projected for 1990 is 243,513,000.* If we want to be overly simplistic, this means that approximately the same number of thoracic surgeons will be needed in 1990 as are active today unless there is a significant change in the work load. Consequently, it would seem that we have about balanced out the supply and demand ratio in our specialty at this point.

Numbers of Thoracic Surgeons

Are we training too many thoracic surgeons? This is a debatable issue, and yet it is possible to have a visceral feeling about it. As a program director, and I have heard this from other directors, I believe that in the past 5 years there has been a change in the number of positions available to the graduates of training programs. In the early 1970s, a resident finishing a thoracic surgical training program had a variety of opportunities available to him. At the present time, the job openings appear to be considerably fewer, and in the classified ads of the November 1979 issue of *The Annals of Thoracic Surgery*, there were 10 surgeons seeking positions and six openings advertised.

How does one resolve this problem? There seems to be no simple answer since there is no mechanism built into the current superstructure of medicine in the United States to regulate the number of training programs. In fact, in certain programs in internal medicine specialties such as cardiology, there is no restriction on the number of trainees in a given program. In thoracic surgical programs, the number of trainees is subject to the approval of the Residency Review Committee and its parent body, the Liaison Committee on Graduate Medical Education (LCGME). However, neither of these committees has a mandate to control the number of programs, and they look at the quality of the program but not the quantity of programs. Although one might be concerned with the attitude of the Federal Trade Commission regarding regulation of numbers of trainees in a given specialty and term that restraint of trade, it is hardly conceivable that allied health personnel will be performing major thoracic or cardiac operations in lieu of a trained, Board-certified thoracic surgeon in the foreseeable future. Someone is going to have to bite the bullet on this issue.

It seems to me that the most effective method of managing our manpower needs is what economist Eli Ginsburg [8] terms a "taut line." This can be accomplished by frequent and reasonably accurate assessments of the work load in thoracic surgery, which is then relayed to the LCGME and the Residency Review Committee. Since our membership in this organization encompasses the majority of practicing thoracic surgeons in the United States, we are in the best position to make these assessments of our work load and our needs. It is my belief that surveys, such as those for the years 1970 and 1976, should be carried out at regular intervals, perhaps every 4 years in order to detect trends that may occur. In the event that it is necessary to reduce the number of trainees, a viable option in terms of everyday management of large case loads is the use of well-trained surgeon assistants. Drs. Miller and Hatcher [11] from Emory University have documented the effec-

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*United States Census Bureau, Washington, DC: Personal communication, 1979.

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tiveness of these allied health personnel, and I believe this is an option to be considered for other institutions in the future.

Federal Agencies

There are two other federal agencies currently pursuing activities that may encroach further upon the traditional freedom in the patient-doctor relationship as well as progress in the field of thoracic surgery. The first is the Food and Drug Administration and its Medical Device Amendments Act enacted in 1976 to control the development and usage of medical devices. Specific regulations will soon be forthcoming from the Food and Drug Administration on the implementation of this law. Some of these regulations may be so restrictive that they inhibit creativity, substantially increase the cost of research in health care, increase manufacturers' liability, and potentially deprive patients of lifesaving devices. Proposed regulations appear in the Federal Register and should be of concern to all of us. As these proposed regulations are published, interested parties or organizations are invited to comment. The Society of Thoracic Surgeons has been well represented by Dr. Arthur Beall in this area. We must continue to be knowledgeable and involved in this because if we do not take a positive position regarding these regulations, the advances in technology and the development of new devices which have been so plentiful over the past several decades may come to a complete halt. The Society of Thoracic Surgeons must act positively or else we will be on the threshold of the dark ages of biomedical engineering.

The other agency whose activities should be of grave concern to the medical profession is the Federal Trade Commission. The Bureau of Competition of the Federal Trade Commission appears to regard the medical profession as a "conspiracy." I shall not attempt to detail the numerous activities that the Federal Trade Commission is pursuing in an ostensible effort to promote competition and stimulate the free market as a mechanism to reduce prices, but with apparent disregard for the quality of health care. No more has this been evident than in their action against the American Society of Plastic and Reconstructive Surgeons regarding advertising and requirements for membership in that society. The perception of the Federal Trade Commission that specialty board certification has been devised to avoid competition rather than to improve the quality of care strikes at the very heart of our quest for excellence in health care and protection of the public. In another action, the Federal Trade Commission found the American Medical Association, the Connecticut State Medical Society, and the New Haven County Medical Society guilty of restraint of trade by restricting physician advertising. While advertising in itself may be of questionable value, a major problem posed by this decision is that there is no built-in mechanism for monitoring and eliminating false and misleading or fraudulent advertising. Unless advertising can be controlled, it could lead to fraud and quackery unknown in the United States since the days of the snake oil salesman. Additionally, there is no evidence at the present time that advertising and increased availability of health care from less qualified physicians or paramedical personnel will actually reduce costs. Our best response to this problem is the education of the public by all means available to recognize the necessity for adequate training and specialty certification in their selection of a physician or surgeon. This should be done by us collectively and individually.

Physician Competence

The final issue I would like to address is that of physician competence. This is a complex issue, and the definition of a competent thoracic surgeon is elusive. In a report of the Committee on Continuing Competence of Physicians to the Coordinating Council on Medical Education of the American Medical Association in June, 1978 [13], the following description of the term *physician competence* was submitted:

> Physician competence is the function of an array of attitudes which compose a pattern of effective activity directed towards the health care and well being of people as individuals or groups. Three essential dimensions are usually recognized and encompass:

a) knowledge—factual knowledge and understanding relating to functions which the physician is called upon to perform.
b) abilities
    1. communication
    2. technical skills
    3. self discipline and work habits
    4. professional attitude
c) clinical judgment—the capacity to apply the appropriate and important knowledge and skills at the right time. Included in this is the synthesis of hypotheses from the data and the appropriate testing of these hypotheses.

Thus, for a thoracic surgeon, a definition of competence may include the fund of knowledge necessary to diagnose and treat diseases of the thoracic cage and its contents and the ability to perform the appropriate operative procedures necessary for diagnosis and treatment of these diseases. Going one step further, we can construct a diagram sometimes called a matrix, which contains on one axis the knowledge and on another the skills necessary. Where these interface could loosely be called judgment. Nevertheless, an adequate mechanism to measure competence or competent performance is extremely difficult to achieve. While admittedly not perfect, the current certifying process of the American Board of Thoracic Surgery is designed to measure these qualities. It could be argued that the ideal measurement of competence would be to have one or two impartial experts observe a surgeon in action for a period of several days. Unfortunately, this is not logistically practical. The certifying process as currently carried out measures knowledge reasonably well by the cognitive examination. The abilities and technical skills cannot be measured by the certifying examination and in this regard the Board is totally dependent upon the judgment of program directors and their associates observing these qualities in the trainee. Clinical judgment is measured partially by the oral examination portion of the certifying vehicle and partially by the evaluation of the program director. The total certifying process has undergone numerous revisions in the past 10 years and is constantly scrutinized, particularly with regard to "content validity," meaning whether or not the examination measures those qualities we are seeking to assess. While this process does not unequivocally prove competency, it is the best vehicle at the present time to assure the profession and the public that the individual who is certified has the knowledge, ability, skills, and judgment to perform the duties of a thoracic surgeon at the time that he is certified.

The recertification process, which has stirred considerable controversy, is simply an extension of the basic mechanism to attempt to assure continued competency of the members of our profession over a period of time. It is not designed as a restrictive or onerous hurdle, but simply a method of attesting that the surgeon is continuing to perform at an appropriate level, be it in cardiac surgery, general thoracic surgery, or both, as is applicable to the practice of the specific individual. I believe that the Committee on Continuing Education in Thoracic Surgery has designed a reasonable method of achieving recertification, but perhaps further input by other members of our profession may improve upon or even simplify a method of measuring and assuring competence. As Harold Liddle [10] put it, "accountability is the name of the game," and there is no question that the public is now asking the medical profession to prove by some mechanism their continued competence. If we do not face this issue squarely and respond to it positively, we are abrogating our responsibility.

Facing the Issues

Finally, I submit to you that the most effective way for the medical profession in general and thoracic surgeons in particular to respond to these issues is to define them and face them. We must eliminate in this organization any semblance of a "town-gown conflict" because the issues are common to us all. This will require greater involvement of the practicing thoracic surgeon in the programs, deliberations, and decisions of the organization. The full-time academician must develop a better understanding of the problems and concerns of those who labor outside university hospitals, without the help of residents and other highly trained support personnel. The Society of Thoracic Surgeons must truly assume its position as the representative voice for our specialty. We have several committees within this organization that are deeply involved with these issues—the Government Relations Committee, the Standards and Ethics Committee, and the Ad Hoc Committee on Manpower. We must all get involved. I suggest that in the future, more time should be allocated at the annual meeting for open discussion of such issues with active participation of the entire membership. We have the opportunity to provide input regarding our position to our related organizations: the American College of Surgeons, the American Board of Thoracic Surgery, the Council of Medical Specialty Societies, the Residency Review Committee, and the American Medical Association. Representatives of The Society of Thoracic Surgeons should provide recommendations and expertise to agencies such as the Food and Drug Administration and the National Council on Health Care Technology. The mechanisms are in place. We must understand the issues and work together to resolve them. We must make ourselves heard as a unified voice representing thoracic surgery, taking a positive position that all can see: the general public, our patients, the rest of the profession, and especially the federal government. Let us not shirk this responsibility because we owe it to them and we owe it to ourselves.

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Intraoperative Esophageal Manometry: Is It Valid?

Mark B. Orringer, M.D., Ronald Schneider, George W. Williams, Ph.D.,
and Herbert Sloan, M.D.

ABSTRACT **Forty-five patients undergoing a Collis-Nissen antireflux operation had preoperative, several intraoperative, and postoperative distal esophageal high-pressure-zone (HPZ) measurements. In 11 patients (24%), intraoperative manipulation of the esophagus alone, prior to beginning the repair, had a major effect upon the HPZ. The final *mean* intraoperative HPZ pressure (21.2 mm Hg) differed significantly ($p < 0.01$) from that obtained postoperatively at 1 to 3 weeks (15.2 mm Hg), 6 months (11.2 mm Hg), and 12 months (12.1 mm Hg). However, there was *no significant statistical correlation* between the final intraoperative HPZ pressures and those obtained after 6 and 12 months. Irrespective of the final intraoperative HPZ value, no patient undergoing acid reflux testing at 6 to 12 months after operation had any gastroesophageal reflux. It is concluded that esophageal manipulation (mobilization or dilation) results in *variable intraoperative* HPZ values that are *not* reliable predictors of HPZ values obtained late postoperatively. The rationale for altering the technique of an operation simply to obtain an "ideal" *intraoperative* HPZ value must be seriously questioned.**

Intraoperative measurement of lower esophageal sphincter pressure was first proposed by Dr. Lucius Hill [2] as a means of ensuring adequate control of gastroesophageal reflux at the time of an antireflux procedure. This is an appealing concept for it suggests that in the operating room, the surgeon may calibrate the distal esophageal high-pressure zone (HPZ) to a specific desirable pressure that will correlate with subsequent postoperative manometric values that have been associated with successful reflux control. Unfortunately, neither of the two previous papers dealing with this subject [1, 2] contained a statistical analysis of the data. This study was undertaken to determine the effects of general anesthesia and operative manipulations of the esophagus on intraoperative HPZ determinations and the statistical relationship between intraoperative and postoperative HPZ values.

Material and Methods

Forty-five adult patients, including 25 men and 20 women, undergoing the combined Collis gastroplasty–360-degree Nissen fundoplication procedure for control of gastroesophageal reflux [5] were included in this study. Forty-four of these patients had gastroesophageal reflux. Of those with esophagitis, 12 had grade II (ulceration), and 8 had grade III (stricture). Eight had undergone prior antireflux operations, and 9 had scleroderma. Eight patients had diffuse esophageal spasm. At the time of the Collis-Nissen procedure, 8 patients underwent intraoperative dilation of strictures, and 8 underwent esophagomyotomy for spasm.

Preoperative esophageal manometry using triple-lumen perfused catheters and standard acid reflux testing with an intraesophageal pH electrode as described previously [3] were performed in 43 of these patients. The same equipment and technique were used for intraoperative HPZ measurements made with the patients under general anesthesia (1) prior to opening the chest in the right lateral decubitus position (38 patients), (2) after mobilizing the distal esophagus and cardia prior to beginning the gastroplasty (37 patients), (3) after completion of the gastroplasty, with the gastric fundus reduced below the diaphragm (29 patients), and (4) following the fundoplication, with reduction below the diaphragm and the posterior crural sutures tied with the chest open (45 patients). Two sequential pullback tracings were made for each determination, and the six HPZ values obtained were averaged to give a single HPZ

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pressure and length. In 10 patients, HPZ pullback tracings were compared with the gastroplasty constructed over a 46F bougie and then a 58F dilator. In these instances, a noncrushing Fogarty aortic clamp was placed on the stomach adjacent to the respective dilator, which was then removed for the manometric study. It was thus possible to contrast HPZ values obtained with gastroplasty tubes of two different sizes in the same patient. The intraoperative HPZ values were compared with postoperative HPZ determinations and acid reflux tests performed without sedation or anesthesia after 1 to 3 weeks (44 patients), 6 months (35 patients), and 12 months (21 patients).

Results

General anesthesia had no major effect upon the HPZ: values obtained after induction of anesthesia, with the chest closed, were not appreciably different from those obtained preoperatively. In 11 patients (24%) (Table 1), dilation of peptic strictures or manipulation of the esophagus required for mobilization of the cardia produced increases in distal esophageal HPZ tone to levels of 50% or more of the final HPZ value obtained at the conclusion of the gastroplasty and fundoplication.

The *mean* HPZ pressures for the entire group obtained at the various intervals before, during, and after operation are plotted graphically in the Figure. Significant differences ($p < 0.10$) in mean values (both pressures and lengths) obtained during operation at each successive stage of the repair were found. Further, the intraoperative pressures correlated significantly ($p < 0.05$).

The HPZ values recorded when the gastroplasty tube was fashioned over a 46F dilator and then a 58F dilator in 10 patients are compared in Table 2. Neither the mean pressures nor the mean lengths obtained with these two gastroplasty tube sizes differed significantly ($p > 0.10$).

The average intraoperative HPZ pressure and length obtained at the conclusion of the Collis-Nissen repair were 21.22 mm Hg ± 1.5 (standard error of the mean) and 5.93 cm ± 0.17, respectively. These HPZ values decreased to 15.2 mm Hg ± 0.73 and 5.18 cm ± 0.16 at 1 to 3 weeks after operation, 11.2 mm Hg ± 0.49, and 4.7 cm ± 0.19 at 6 months post-

Table 1. Marked Effect of Esophageal Manipulation on High-Pressure-Zone Values in 11 Patients

	HPZ before Operation		HPZ under General Anesthesia								HPZ after Operation					
			Chest Closed		Cardia Mobilized		Gastroplasty Complete		Repair Complete		1 to 3 Wk		6 Mo		12 Mo	
Patient No.	P	L	P	L	P	L	P	L	P	L	P	L	P	L	P	L
1	3	1	26[a]	2	25	5	...	...	34	6	13	6	15	6	12	6
2	0	0	28[a]	3	29	4	34	5	59	7	18	6	12	4	10	3
3	5	2	...	...	10	3	...	...	14	4	12	4	...	...	...	...
4	9	3	3	2	12	6	15	6	14	6	23	4	15	5	9	4
5	9	3	...	...	13	3	32	4	22	6	16	4	10	4	10	3
6	0	0	...	...	13	2	18	4	23	9	28	7	16	6	21	8
7	6	5	8	3	14	6	16	5	17	5	12	6	6	5	6	7
8	3	1	10	2	15	4	15	5	18	6	13	5	...	...	...	...
9	0	0	0	0	7	4	9	4	15	5	9	5	6	3	...	...
10	8	4	5	4	7	5	8	5	13	6	12	5	8	5	...	...
11	0	0	0	0	6	5	0	0	12	7	10	5	7	4	...	...

[a] After dilating distal stricture.

HPZ = high-pressure zone; P = HPZ pressure in mm Hg; L = HPZ length in centimeters.

Table 2. Effect of Gastroplasty Tube Size on High-Pressure-Zone Values

	46F Tube		58F Tube	
Patient No.	HPZ Pressure (mm Hg)	HPZ Length (cm)	HPZ Pressure (mm Hg)	HPZ Length (cm)
1	24	6	20	7
2	6	5	13	6
3	33	6	19	4
4	15	9	15	6
5	30	7	23	6
6	13	6	15	6
7	54	6	34	5
8	50	8	48	12
9	32	5	32	4
10	17	7	12	8

HPZ = high-pressure-zone.

operatively, and 12.1 mm Hg ± 0.85 and 4.8 cm ± 0.31 at 12 months postoperatively. Except for the difference between the 6- and 12-month determinations, the differences between all the mean pressures and lengths are highly significant ($p < 0.1$). While final intraoperative HPZ pressures and lengths correlated significantly with those obtained after 1 to 3 weeks, there was no significant statistical correlation between the final intraoperative HPZ pressures and those obtained after 6 months and at 12 months.

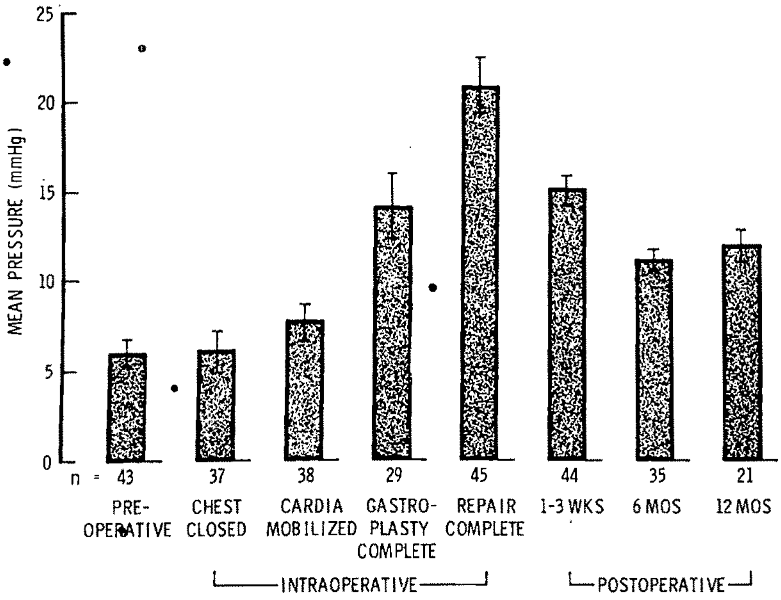
Comment

Previous discussions of intraoperative manometry have dealt with *mean* distal HPZ pressures obtained in the groups of patients being evaluated [1, 2]. As in these studies, our data indicate that mean HPZ values obtained after induction of general anesthesia are not significantly different from those determined preoperatively. Further, like others [1, 2], we have found that mean intraoperative HPZ pressures obtained for the group at the completion of the antireflux procedure are approximately twice as high as subsequent mean recordings obtained 6 and 12 months after operation.

However, after the intraoperative data are evaluated in more detail and subjected to statistical analysis, the errors inherent in relying on intraoperative determinations become apparent. By repeating HPZ measurements after mobilization of the cardia but prior to construction of the gastroplasty tube, we found that operative manipulation of the lower esophagus and esophagogastric junction can result in contraction of esophageal smooth muscle similar to that which occurs when the small intestine is momentarily compressed between the fingers. Thus, in one-quarter of our patients (see Table 1), after the cardia was mobilized but before the gastroplasty was begun, distal esophageal HPZ values were 50% or more of the final intraoperative HPZ pressures obtained when the repair was complete. Dilating distal strictures in Patients 1 and 2 (see Table 1) produced HPZ determinations of 26 and 28 mm Hg, respectively.

It is therefore apparent that an intraoperative HPZ value obtained at the completion of an antireflux operation is a reflection not only of the increased distal esophageal pressure resulting from a fundoplication, but also of a highly variable response of the lower esophageal muscle to dilation and manipulation. Uncertain as to the importance of an absolute intraoperative HPZ determination, we did not alter the technique of the Collis-Nissen operation in any patient from that which we have described [5] or make any intraoperative adjustments in the gastroplasty or fundoplication in order to achieve an "ideal" intraoperative pressure. This approach was justified by the fact that despite the relatively wide range of final intraoperative HPZ values in our patients (10 to 59 mm Hg; average, 21.2 mm Hg), measurements at 6 and 12 months were far less scattered. HPZ values at 6 months ranged from 6 to 17 mm Hg (average, 11.2 mm Hg), and at 12 months, from 6 to 21 mm Hg (average, 12.1 mm Hg). Further, and more important, no patient undergoing an acid reflux test at 6 or 12 months after operation had any evidence of gastroesophageal reflux, regardless of the final intraoperative HPZ values.

Cooper and associates [1] found that the average HPZ value in their 11 patients at 1 week after operation (21 mm Hg) was approximately one-half the final intraoperative value obtained



Mean high-pressure-zone pressures (± standard error of the mean) at various intervals before, during, and after Collis-Nissen operation. (n = total number of patients in each group.)

and that it changed little during the first postoperative year. Our data suggest that within the first 1 to 3 weeks after operation, the artifactual hypertonicity of the newly constructed HPZ evident intraoperatively persists and that only subsequently does this "spasm" subside to pressures roughly one-half of the final intraoperative values.

As done by Cooper and associates [1] we, too, can construct a graph of *mean* HPZ values for our patients undergoing intraoperative determinations (see Figure). Cooper's HPZ values, obtained with the Honeywell MP-3 catheter, are nearly twice as high as ours, obtained with standard perfused catheters. In both of our series, however, there is a drop at 12 months to values that are about one-half of the final intraoperative pressures. However, it is incorrect to conclude from these data that because subsequent mean HPZ values 6 and 12 months after operation are approximately one-half (about 12 mm Hg) of those obtained intraoperatively after completion of a Collis-Nissen repair, we should strive for an intraoperative value of approximately 24 mm Hg. The data reported here reflect *mean* values obtained for the entire *group* of patients. If intraoperative and subsequent postoperative HPZ pressures obtained in *individuals* are compared statistically, *no significant correlation* is found. This applies not only to our data, but also to those presented by Cooper and associates [1] as well. In other words, one cannot reliably predict from an intraoperative HPZ value in a given patient what the ultimate pressure will be one year later.

One explanation offered for the unsatisfactory reflux control we reported for the combined Collis-Belsey procedure [4] was the size of the dilator we used for construction of the gastroplasty. Because of some problems with esophageal emptying after constructing a gastroplasty over a 50F bougie, as originally described by Pearson and Henderson [7], we began to use a 58F dilator for the gastroplasty. Pearson [6] thought that a gastroplasty tube constructed over a 58F bougie has far less "tone" than one formed over a 50F dilator, and that "the luminal diameter is critically related to the pressure we create in the distal esophagus." Our experience does not entirely support these findings. In the 10 patients in whom we obtained sequential pullback tracings through 46F and then 58F gastroplasty tubes (using a Fogarty aortic clamp placed on the stomach adjacent to the dilators), neither gastroplasty tube pressures nor lengths of the two sizes were significantly different (see Table 2). We believe that it is the completeness of the fundoplication, rather than the size of the gastroplasty tube per se, that provides the critical increased lower esophageal sphincter pressure responsible for reflux control after performing a gastroplasty.

We have found that intraoperative esophageal manometry adds a minimum of 30 to 45 minutes to an antireflux operation. While it is encouraging to watch the distal esophageal HPZ evolve intraoperatively as the gastroplasty tube is constructed and then the fundoplication is performed, the information gained is of little practical or statistical significance. For intraoperative HPZ values can be unpredictably affected by manipulation of the esophagus during mobilization, dilation of the stricture, and by the amount of air in the stomach at the time of the measurement. Finally, because the HPZ achieved with an antireflux procedure is not necessarily symmetrical, pullback tracings using a single-lumen catheter as proposed by Hill [2] may not necessarily indicate "satisfactory" values unless the side opening of the recording catheter is oriented toward the point of maximum intraesophageal pressure created by the operation. Using triple-lumen perfused recording catheters with side holes, we rarely see identical HPZ profiles in all three recording channels.

There is more to achieving satisfactory long-term control of reflux than simply establishing a given HPZ value in the operating room. The length of the HPZ constructed, the degree of inflammation of the distal esophageal tissue around which the fundoplication is performed, and the tension under which the distal esophagus is placed are all important. We conclude that intraoperative HPZ values alone cannot be used to predict reliably the future success of an antireflux operation.

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Discussion

DR. R. ILVES: (Toronto, Ont, Canada): Dr. Orringer is to be commended on maintaining a healthy skepticism on procedures touted as essential by others. As he mentioned, we at the Toronto General Hospital have also been making similar measurements preoperatively, intraoperatively, and postoperatively. Some of our observations and measurements agree with those he reported; others are at variance.

We have also studied patients by placing vascular clamps against different sizes of Maloney bougies to simulate various diameters of gastroplasty tubes. Our measurements indicated that the larger the diameter of the gastroplasty tube, the lower the intraluminal pressure. In this report from Ann Arbor, six out of ten measurements show decreased pressure with larger tubes, two remain the same, and two increase slightly. The only major changes, however, are two that drop significantly.

We have also studied the effects of general anesthesia, both with the chest closed and the chest open, and after mobilization of the gastroesophageal junction. Most patients show a fairly consistent and unchanging level of sphincter pressure, although a few of them show substantial changes.

In the Ann Arbor series, there are 8 patients with diffuse spasm. How many of these, if any, are included in the 11 patients measured after esophageal mobilization is not stated. As you know, this condition is notorious for producing spasm with manipulation, and, of course, it is a completely different entity from reflux disease. We specifically excluded primary motor disorders in our series.

Other general comments are pertinent. As anyone who analyzes motility results is aware, the exact level of high-pressure-zone measurement is very subjective. Thus, while statistical manipulation may show significance, it is evident that in none of Dr. Orringer's patients studied after esophageal mobilization is there a meaningful change. The change from zero to 7 mm, for instance, may be statistically significant but is lower nevertheless.

Dr. Orringer is quite correct in stating that the mean values for many patients studied intraoperatively and postoperatively are correlated, but that for any individual patient no significant correlation can be found.

The series of 62 patients with reflux whom we studied is now past 14 months on the average, ranging from one to four years. The clinical results in this group are as follows: 37, excellent; 19, good; and 5, no improvement. These 5 are specifically not improved because they had dysphagia. It is evident, though, that the intraoperative values and postoperative values do not correlate in individual patients. Some of the highest values intraoperatively went down fairly low postoperatively, and the patients with good and excellent results can be compared with those with no improvement. There is no difference statistically between these two groups. Also, there was no significant difference in high-pressure zone between the excellent, good, and poor groups, either intraoperatively or on follow-up. None of our unimproved patients show recurrent reflux on follow-up.

I had the pleasure of spending last year with Dr. Lucius Hill in Seattle. As a result, I think I have developed a good understanding of many things about his operation. First, that particular procedure is the only one that truly lends itself to intraoperative adjustment. The tightening or loosening of sutures does alter the pressure in the gastroesophageal junction area reliably. With both the Nissen and Belsey operations, if intraoperative pressures do prove to be meaningful, the entire fundoplication would have to be redone, a truly distressing thought.

Second, I fully agree that the high-pressure zone, either preoperatively or postoperatively, is not symmetrical. Dr. Hill's gastropexy produces a rather ovoid slitlike esophagogastric junction. However, his single-lumen manometry tube is similarly ovoid in shape and reliably aligns itself in the same axis within the repair. We proved this intraoperatively by trying to rotate the catheter to any other position. Thus, one would anticipate consistency in his values. Using a circular triple-pressure probe setup, I found, as might be expected, definite asymmetry in one Hill repair I did recently.

Intraoperative manometry has been of direct benefit in some of our patients with primary motor disorders. In those with diffuse spasm, it has reliably indicated the level to which a myotomy needs to be carried. It also helps locate the area of obstruction in redo operations in patients with achalasia.

Intraoperative manometry may not be the ideal tool for helping produce better, more predictable results. It is too soon to tell. Our follow-up may be too short; that of Dr. Orringer and associates certainly is. However, the search for some method to achieve such results remains the responsibility of the practicing academic surgeon.

DR. ORRINGER: I thank Dr. Ilves for his comments. In response to his question regarding the effect of primary esophageal spasm on intraoperative measurements, among our 11 patients (the 24% who had a significant intraoperative increase in the high-pressure zone simply from manipulating the esophagus), only 1 had primary esophageal spasm. But I do not think that we can exclude this group of patients from our population because, in fact, many patients with esophageal spasm also have concomitant gastroesophageal reflux. If this technique of intraoperative esophageal manometry is valid, it should have applicability to this population as well; and it simply does not.

I will conclude by emphasizing that in our enthusiasm to be more objective in evaluating esophageal disease, we must be aware of the limitations of our different diagnostic techniques. There is variability in the results obtained in an individual patient depending on the different manometric system used—the perfused catheter versus the nonperfused catheter versus the Honeywell MP-3 catheter with built-in microtransducers. In addition, the effect of esophageal manipulation that I have seen in a quarter of the patients whom I have studied is something that must apply to all operations on the distal esophagus regardless of the type, whether it is the combined Collis-Nissen operation, the Hill hiatal hernia repair, or another one. Because manipulation clearly has an effect on recorded intraoperative esophageal pressures, I continue to believe that the primary value of manometry in evaluating gastroesophageal reflux is its localization of the lower esophageal sphincter for accurate placement of the intraesophageal pH electrode for acid reflux testing and pH monitoring. Documented reflux control, as determined by the pH electrode rather than an isolated distal esophageal high-pressure-zone value, is currently the best indicator of a successful antireflux operation.

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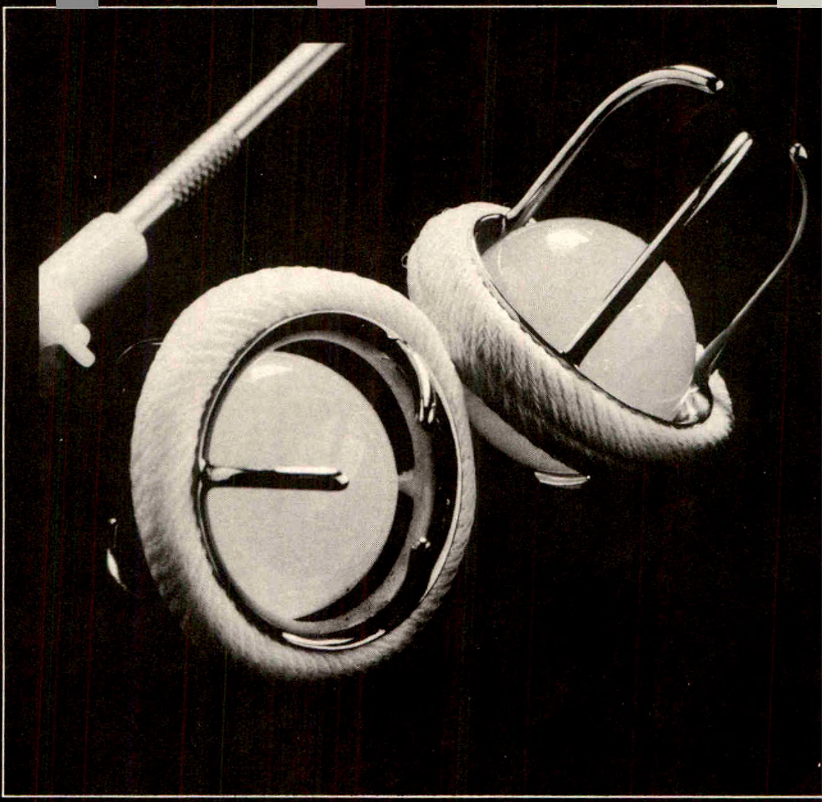

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Among newer cephalosporins, only Mandol has in vitro activity[*] against *H. influenzae* comparable to that of chloramphenicol and superior to that of ampicillin.[3]

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1 g (equivalent to cefamandole activity) in 10 and 100-ml-size vials.

Demonstrated increased in vitro activity[*] against *Enterobacter*[†] as compared with other cephalosporins.[4]

In vitro activity[*] against gram-positive organisms, including *Staphylococcus aureus, S. epidermidis,* beta-hemolytic and other streptococci,[†] and *Streptococcus pneumoniae.*

Mandol provides in vitro activity[*] against anaerobes.[‡]

Achieves therapeutic levels in pleural and joint fluids, in bile and bone.[§]

May be administered both I.M. and I.V.

---

[*] In vitro activity is not necessarily indicative of clini
effectiveness.

[†] *Pseudomonas, Acinetobacter calcoaceticus* (form
Mima and Herellea species), most *Serratia,* enter
(e.g., *S. faecalis*), and some strains of *P. vulgaris* a
resistant in in vitro tests. Initially susceptible strair
Enterobacter may occasionally become resistant
therapy.

[‡] Most strains of *Bacteroides fragilis* are resistant ir
however, infections caused by susceptible strains
been treated successfully.

[§] Tissue analysis gives primarily qualitative rather t
meaningful quantitative data as to the presence or
absence of an antibiotic in a particular body fluid c
tissue. Therapeutic efficacy cannot be predicted b
level attained in a specific body fluid or tissue.

Note: Mandol should be given cautiously to penicillin-sensitive patients and is contraindicated patients with known allergy to cephalosporins.

References:
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3. Antimicrob. Agents Chemother., 8:91, 1975.
4. Antimicrob. Agents Chemother., 9:994, 1976.

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See reverse side for summary of prescribing information.

MANDOL® I.M./I.V.
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Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Mandol is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, *Klebsiella* species, *Staphylococcus aureus* (penicillinase and non-penicillinase-producing), beta-hemolytic streptococci, and *Proteus mirabilis*

Urinary tract infections caused by *Escherichia coli*, *Proteus* species (both indole-negative and indole-positive), *Enterobacter* species, *Klebsiella* species, group D streptococci (*Note:* Most enterococci, e.g., *S. faecalis*, are resistant), and *S. epidermidis*

Peritonitis caused by *E. coli* and *Enterobacter* species

Septicemia caused by *E. coli*, *S. aureus* (penicillinase and non-penicillinase-producing), *S. pneumoniae*, *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae*, and *Klebsiella* species

Skin and skin-structure infections caused by *S. aureus* (penicillinase and non-penicillinase-producing), *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae*, *E. coli*, *Enterobacter* species, and *P. mirabilis*

Bone and joint infections caused by *S. aureus* (penicillinase and non-penicillinase-producing)

Clinical microbiologic studies in nongonococcal pelvic inflammatory disease in females, lower respiratory infections, and skin infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Mandol has been used successfully in these infections in which several organisms have been isolated. Most strains of *Bacteroides fragilis* are resistant in vitro; however, infections caused by susceptible strains have been treated successfully.

Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefamandole. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, Mandol may be used concomitantly with an aminoglycoside (*see* Precautions). The recommended doses of both antibiotics may be given, depending on the severity of the infection and the patient's condition. The renal function of the patient should be carefully monitored, especially if higher dosages of the antibiotics are to be administered.

Antibiotic therapy of beta-hemolytic streptococcal infections should continue for at least ten days.

Contraindication: Mandol is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY WITH MANDOL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

In newborn infants, accumulation of other cephalosporin-class antibiotics (with resulting prolongation of drug half-life) has been reported.

Precautions: Although Mandol rarely produces alteration in kidney function, evaluation of renal status is recommended, especially in seriously ill patients receiving maximum doses.

Prolonged use of Mandol may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly). There may be a false-positive test for proteinuria with acid and denaturization-precipitation tests.

As with other broad-spectrum antibiotics, hypoprothrombinemia, with or without bleeding, has been reported rarely, but it has been promptly reversed by administration of vitamin K. Such episodes usually have occurred in elderly, debilitated, or otherwise compromised patients with deficient stores of vitamin K. Treatment of such individuals with antibiotics possessing significant gram-negative and/or anaerobic activity is thought to alter the number and/or type of intestinal bacterial flora, with consequent reduction in synthesis of vitamin K. Prophylactic administration of vitamin K may be indicated in such patients, especially when intestinal sterilization and surgical procedures are performed.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Usage in Infancy—Mandol has been effectively used in this age group, but all laboratory parameters have not been extensively studied in infants between one and six months of age; safety of this product has not been established in prematures and infants under one month of age. Therefore, if Mandol is administered to infants, the physician should determine whether the potential benefits outweigh the possible risks involved.

Adverse Reactions: *Hypersensitivity*—Maculopapular rash, urticaria, eosinophilia, and drug fever have been reported. These reactions are more likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—Thrombocytopenia has been reported rarely. Neutropenia has been reported, especially in long courses of treatment. Some individuals have developed positive direct Coombs tests during treatment with the cephalosporin antibiotics.

Liver—Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been noted.

Kidney—Decreased creatinine clearance has been reported in patients with prior renal impairment. As with some other cephalosporins, transitory elevations of BUN have occasionally been observed with Mandol; their frequency increases in patients over 50 years of age. In some of these cases, there was also a mild increase in serum creatinine.

Local Reactions—Pain on intramuscular injection is infrequent. Thrombophlebitis occurs rarely.

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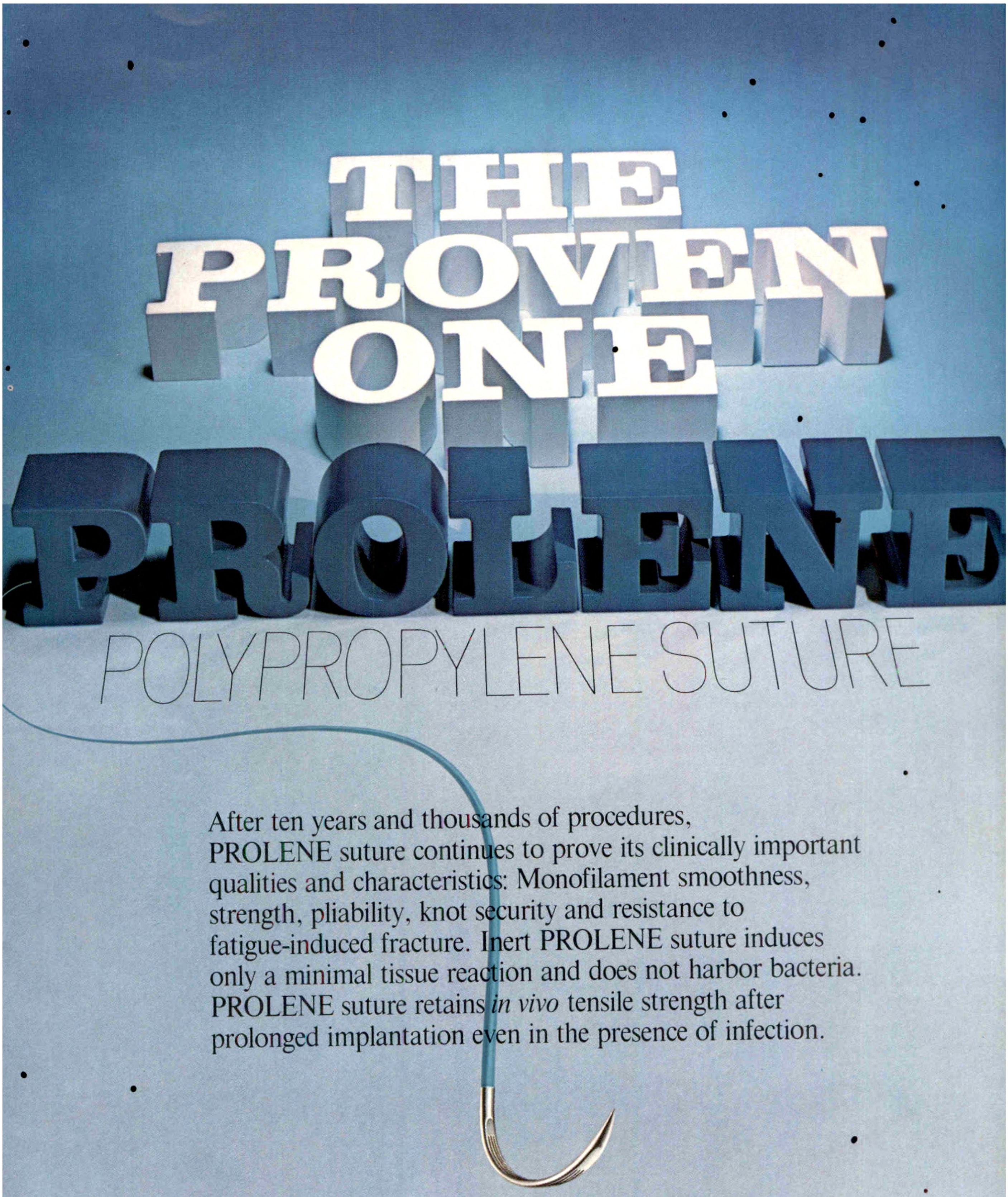

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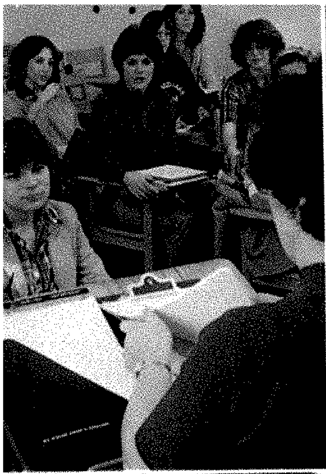
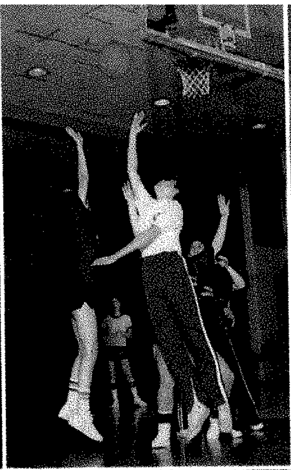

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The indications for permanent pacing in the presence of acute myocardial infarction have not yet been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, mechanism of the arrhythmias, and response to therapy. In general, symptomatic drug-resistant bradyarrhythmias which impair cardiac output are considered indications for pacing in patients with acute myocardial infarction, regardless of infarct location.

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Bacteremia after Esophageal Dilation: A Clinical and Experimental Study

E. S. Golladay, M.D., J. J. Tepas III, M.D., L. R. Pickard, M.D.,
J. J. Seibert, M.D., R. W. Brown, M.D.,
and J. Alex Haller, Jr., M.D.

ABSTRACT **Patients with esophageal stricture caused by caustic ingestion, reflux esophagitis, or esophageal anastomosis often require repeated dilation. These patients frequently have a short febrile course after dilation. After development of brain abscess following esophageal dilation in 1 patient, positive blood cultures were obtained in 4 patients immediately following esophageal dilation. Caustic strictures were produced in cats and esophageal dilations performed. Blood cultures were positive at one minute after dilation in 6 cats and at five minutes in 2 of those cats. The organism responsible in all clinical and three of four experimental examples was *Staphylococcus aureus.* It is suggested on the basis of this clinical and experimental data that patients undergoing esophageal dilation should have prophylactic coverage if they are immunosuppressed, if endocarditis prophylaxis is necessary, if they are infants, if they are diabetic, or if they had severe bacteremia following dilation.**

Approximately 5,000 esophageal burns occur each year in the United States. Ten percent of these result in strictures [3]. Esophageal anastomoses particularly following esophageal atresia have a high incidence of postoperative stricture [4]. Gastroesophageal reflux, which is being recognized with increasing frequency, leads to stricture formation in 2 to 5% of patients [7]. Currently, the preferred initial management of these strictures is repeated esophageal dilation. Although a febrile response in the period immediately after dilation is common and although metastatic abscess has been identified occasionally [2], there is no established precedent for use of antibiotic prophylaxis during esophageal dilation.

Material and Methods

The esophagus of the cat has a wall thickness comparable to that of a human. The lower third is composed of smooth muscle and therefore resembles a child's esophagus more closely than other readily available experimental animals.

Six cats with an average weight of 5 kg were anesthetized with intravenously administered thiamylal sodium. A 12F balloon catheter was passed down the esophagus into the stomach, inflated, and drawn back to the gastroesophageal junction. A second balloon catheter, which was tied 2 cm proximal to the first, was then inflated (Fig 1). Five N sodium hydroxide solution was instilled into the esophageal lumen between the inflated balloons and left in contact with the mucosal surface for two minutes. After irrigation with distilled water, the area was washed with 1% acetic acid.

All of the animals in the initial series died at 10 days secondary to inanition. Therefore a Stamm gastrostomy was performed at the time of the burn in an additional 6 cats. Dysphagia occurred routinely in the first 72 hours, and many animals appeared quite ill. If insufficient food or water was ingested, the animals were fed by gastrostomy. They were given 2 ml of Combiotic (penicillin and streptomycin) intramuscularly twice daily for 5 days to prevent aspiration pneumonia.

Postmortem examination was done on all animals that died. The histology of the esophagus was consistent with that of the time interval after the burn in each of the animals (Fig 2). An esophagogram obtained 21 to 28 days after the

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From the Departments of Surgery, Radiology, and Pathology, University of Arkansas Medical Sciences Campus and Arkansas Children's Hospital, Little Rock, AR, and the Division of Pediatric Surgery, the Johns Hopkins Hospital, Baltimore, MD.

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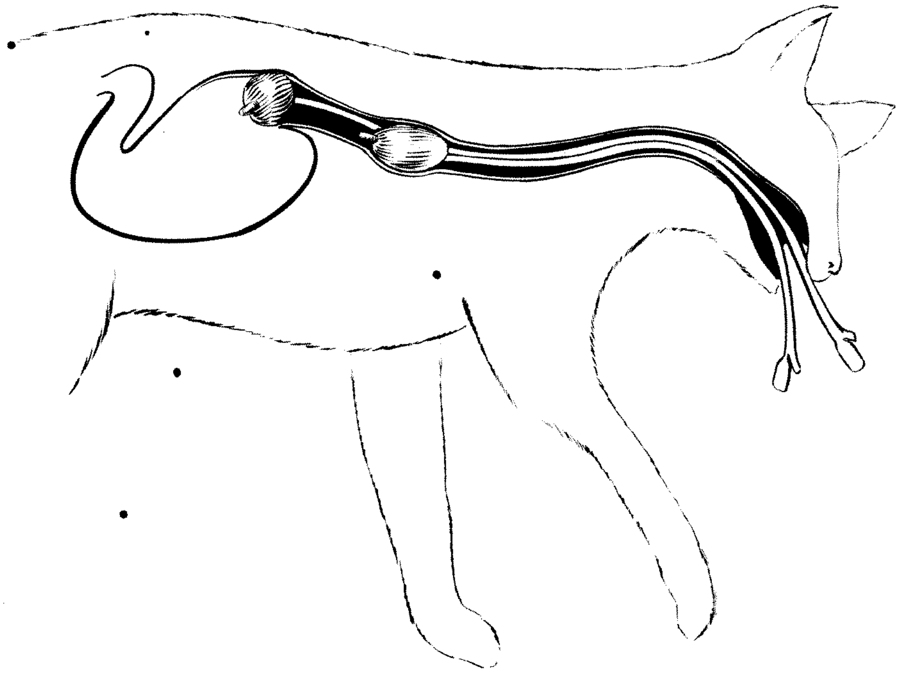
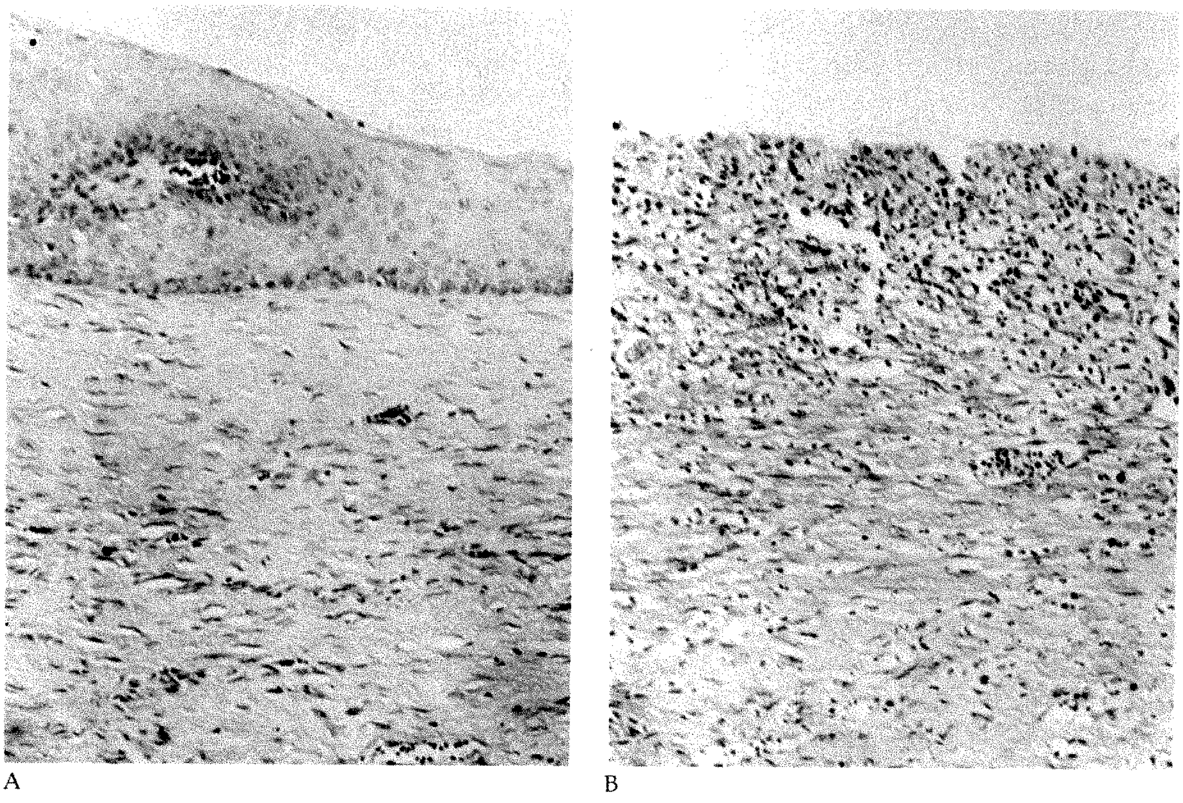


Fig 1. Experimental design for esophageal burn at the gastroesophageal junction with balloon catheters.



A

B

Fig 2. Histological appearance 28 days after the esophageal burn demonstrates resurfaced esophageal mucosa (A) adjacent to esophageal ulceration (B). (Both: H&E; original magnification ×100.)

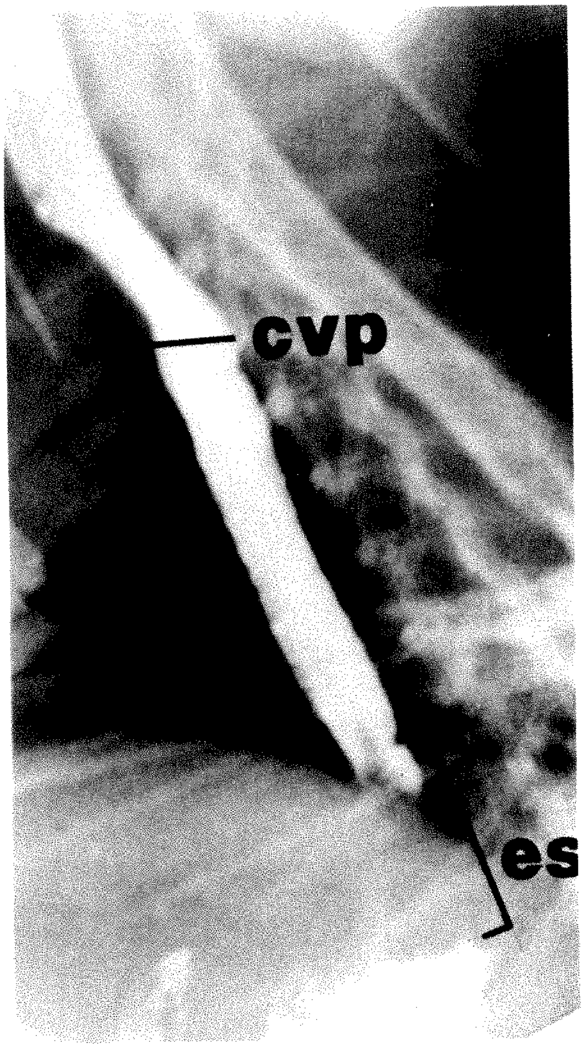


Fig 3. Roentgenogram with central venous line placement (cvp) *and esophageal stricture* (es) *demonstrated.*

burn verified stricture in each of the animals. No other medications were administered, nor was dilation performed prior to completion of the 28-day period. None of the second group of animals died of pneumonia or mediastinitis.

Twenty-eight days after the esophageal burn, a central venous line was placed through an internal jugular cutdown and its position verified by chest roentgenogram (Fig 3). Retrograde esophageal dilations were performed using Tucker dilators that had been scrubbed with 7.5% povidone-iodine solution for five minutes prior to dilation. Blood cultures were obtained on each of the cats prior to dilation as well as one minute and five minutes after dilation.

Results

By roentgenographic and histological confirmation, the technique produced a caustic stricture in an animal with defined limits both in location and depth. The subsequent dilation produced positive blood cultures at one minute in 4 of 6 cats. Two of these 4 had continuing positive blood cultures at 5 minutes. *Staphylococcus aureus* was the organism isolated in three of the four positive one-minute cultures and one of the two five-minute cultures. The remaining positive one- and five-minute cultures grew *Pseudomonas aeruginosa.*

Clinical Experience

The patient who prompted this investigation sustained a documented bacteremia and a resulting metastatic abscess. This 6½-year-old boy was admitted to the Johns Hopkins Children's Medical and Surgical Center in April, 1975, for retrograde dilation of a caustic esophageal stricture (Fig 4). He had been seen

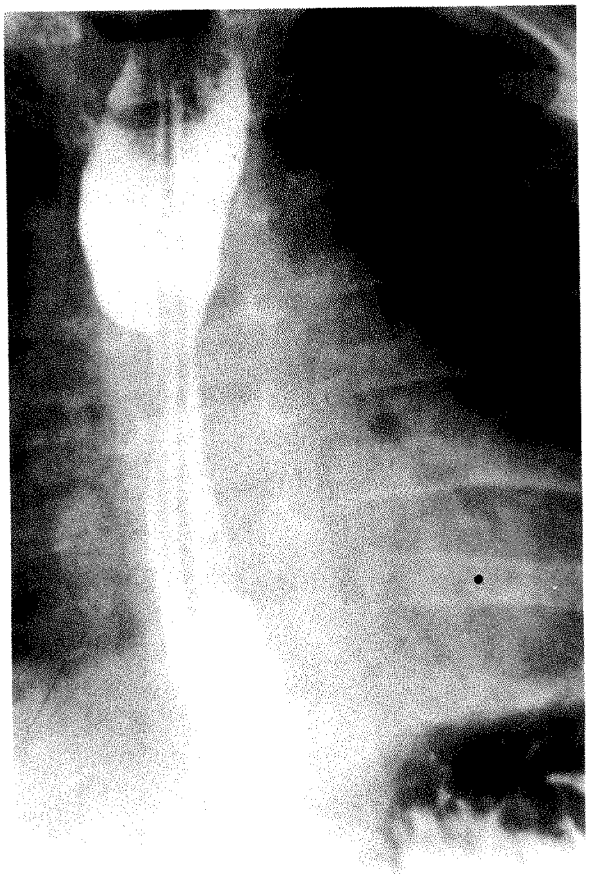


Fig 4. Barium swallow shows midesophageal stricture and a retrieval line in place.

originally in August, 1974, with an esophageal perforation secondary to lye ingestion. Prior to admission in April, 1975, he had undergone seven dilations without problem although he had a febrile response with each dilation.

For 3 days after dilation, he had temperatures to 40°C, complained of headaches, and became progressively lethargic. An echoencephalogram demonstrated a midline shifted 7 mm to the right. Computerized axial tomography demonstrated left cerebral swelling. Because of a questionable history of a fall, it was postulated that he had localized edema secondary to a concussion. A regimen of orally administered dexamethasone, 2 mg every 6 hours, was started. During this 5-day course, the child's fever and lethargy continued. On the sixth postoperative day, a dilated left pupil and bilaterally positive Babinski reflexes developed. A transfemoral cerebral angiogram demonstrated a large avascular mass in the left posterior temporal area. This mass was approached through a left temporal bur hole and 40 ml of gram-positive pus was removed. Cultures confirmed *Staphylococcus aureus* as the infecting organism.

After a two-week course of chloramphenicol, methicillin, and dexamethasone, the patient had recovered completely and was discharged. Three weeks later, he was again admitted for esophageal dilation. Blood culture drawn immediately following dilation grew *Staphylococcus aureus* again. Following this experience, 9 children at the Johns Hopkins Hospital and Arkansas Children's Hospital underwent retrograde esophageal dilation during this study. Five of these children were dilated for caustic stricture, 3 for anastomotic stricture, and 1 for a peptic stricture secondary to gastroesophageal reflux. Each child was dilated under general anesthesia using Tucker dilators and an internalized retrieval line as described in another publication [11]. Dilation was done once in 2 patients, twice in 2, four times in 1, five times in 1, nine times in 1, eleven times in 2, and thirteen times in 1. Blood cultures were consistently positive for *Staphylococcus aureus* in 4 children, 3 with caustic stricture and 1 with a stricture from gastroesophageal reflux. Five children never had positive cultures.

Comment

The occurrence of bacteremia during a variety of manipulative procedures is well known. Bacteremia commonly occurs after dental manipulation, and other techniques such as proctoscopy have occasionally been associated with bacteremia. Two cases of *Pseudomonas* septicemia following fiberoptic endoscopy with esophageal biopsy have been reported in patients with acute leukemia [1]. Bacteremia following urological instrumentation is also well known [10]; usually the organisms are introduced through contaminated water used for lavage. Although Raines and associates [6] and Green and colleagues [1] suggested instrument contamination as the cause of bacteremia following esophageal dilation, the dilators used in both the clinical and experimental aspects of the present study were sterile.

Rontal and associates [8] reported metastatic abscesses as complications of retrograde esophageal dilation. Metastatic brain abscess developed in their first patient. The patient had intravenously administered penicillin and tetracycline circulating at the time of the bur hole, and the abscess was sterile. In our patient, the stricture was dilated initially without antibiotic prophylaxis and a *Staphylococcus aureus* brain abscess developed. Interestingly, in the second patient reported by Rontal and co-workers [8], *Staphylococcus aureus* coagulase-positive osteomyelitis of the left ankle developed.

Rontal and associates [8] suggested that steroids delay scarring of the mediastinum, thus predisposing to bacteremia. In 2 of our patients with documented bacteremia, no steroids were used.

Bacteremia involving *Streptococcus viridans* and a non-hemolytic *Streptococcus* species was documented by Stephenson and associates [9] in 6 of 11 patients undergoing esophageal dilation with Hurst bougies. In 10 volunteers undergoing dilation with the same dilator, no bacteremia was found.

The esophagus usually contains low bacterial counts. However, in instances of stricture with partial obstruction, local bacterial overgrowth might occur. As Raines and co-workers [5] pointed out, esophageal dilation partially disrupts the esophageal lining and therefore resembles a biopsy procedure in producing an entry point for bacteria into the circulation. Review of the existing literature confirms our experimental and clinical impression that bacteremia following esophageal dilation is a common occurrence and the organism most often encountered is a gram-positive *Staphylococcus* or *Streptococcus* species. Accordingly, patients receiving immunosuppressive drugs, those on a regimen of steroids, those with diabetes mellitus, those who are infants in the first six months of life, those who are immunosuppressed for any reason, or those with valvular heart disease should certainly have prophylactic antibiotic coverage with an agent effective against these gram-positive organisms before they undergo esophageal dilation. For those patients who show a prolonged and intense febrile response after dilation, thereby suggesting a clinically important bacteremia, blood cultures should be grown and appropriate antibiotics administered if repeat dilations are necessary.

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Intraoperative Fine Needle Aspiration Biopsy of Thoracic Lesions

Walter J. McCarthy, M.D., Miriam L. Christ, M.D.,
and Willard A. Fry, M.D.

ABSTRACT **Forty-one intraoperative fine needle aspiration biopsies were performed on 35 patients during exploratory thoracotomy (33 patients) or mediastinoscopy (2 patients). Each biopsy was done with a 22 gauge needle. Smears were prepared at the operating table, air-dried, sent directly to the laboratory, stained, and interpreted immediately by the pathologist. Preparation and reporting time averaged ten minutes. Surgical decisions were made on the basis of the pathologist's reports.**

Intraoperative fine needle aspiration biopsy was 100% accurate in differentiating inflammatory from neoplastic lesions. Ninety-five percent diagnostic accuracy for malignancy (39 out of 41 specimens) was obtained. It permitted quick biopsy of lesions deep within the lung parenchyma without the need to cut across uninvolved tissue, thus permitting appropriate resection in each patient. There were no deaths related to the procedure.

At exploratory thoracotomy for suspected lung neoplasm, the surgeon is faced first with the need for an accurate diagnosis. However vigorous the preoperative evaluation, some patients come to operation with an undiagnosed mass or with disease more advanced than anticipated. Surgical judgment varies on the definition of a resectable lesion and the extent of resection indicated, but every surgeon desires exact determination of the diagnosis and a confirmation of the presence or absence of central lymph node involvement at the time of thoracotomy.

Over the past three years, besides using the standard intraoperative frozen-section techniques, we have used fine needle aspiration biopsy with rapid cytological analysis to help in decision-making during thoracotomy. The purpose of this presentation is to report our experience with this intraoperative technique in 35 patients and to discuss its merits and limitations.

Material and Methods

Fine needle aspiration biopsies were taken at thoracotomy from 33 patients and at mediastinoscopy from 2 patients. The biopsy technique was used under three general circumstances. First, 28 lung lesions and 1 mediastinal tumor not diagnosed preoperatively were aspirated as soon as the chest was opened in order to establish or clarify a primary diagnosis. Second, suspicious lymph nodes in the hilum or mediastinum were biopsied ten times in patients with a diagnosis of lung cancer, in order to determine the extent of disease and to define resectability. Third, in 2 patients with lung cancer undergoing staging mediastinoscopy, firm, fixed masses, which we hesitated to biopsy with standard cutting forceps, were biopsied by fine needle aspiration technique to minimize any chance of hemorrhage. Conventional frozen sections were done when convenient or appropriate. Fine needle aspiration biopsy of lung masses was used preferentially for lesions deep within the lung parenchyma that we considered technically difficult to biopsy with ease and safety by standard wedge resection techniques.

Our operative sampling technique and smear preparation are performed by the surgeon (Fig 1). A 22 gauge needle is attached to a 20-ml disposable plastic syringe, which is then fitted into a syringe pistol.* Those items as well as the glass slides to be used are all sterile. If a syringe pistol is not available, manual retraction works well, using either a 10 ml or a 20 ml syringe. The

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*Cameco syringe pistol, Precision Dynamics Corp, 3031 Thornton Ave, Burbank, CA 91504.

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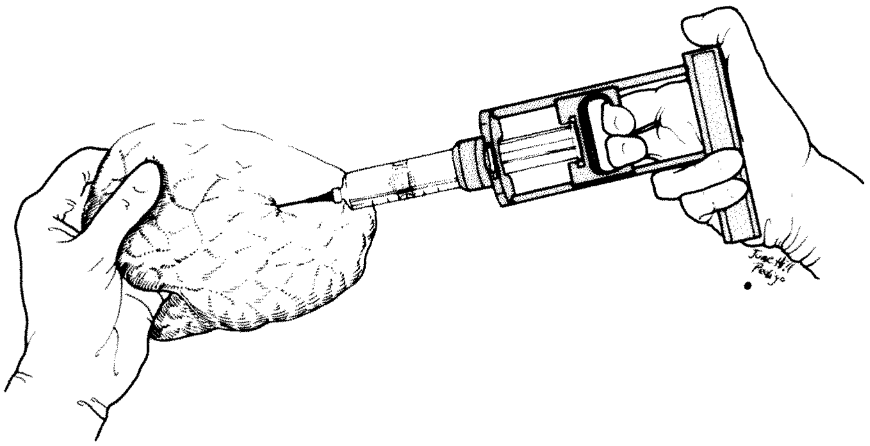

Fig 1. Performing the aspiration. The syringe pistol enables the surgeon to fix the mass with one hand while exerting a vacuum to the syringe with the other.

needle is guided into the lesion, and the piston is retracted to create a vacuum in the syringe. Several short, jabbing motions are made to sample different parts of the lesion. The piston is then relaxed and the needle withdrawn. Most of the specimen is contained within the needle at this time.

The needle is then disconnected from the syringe. The syringe is filled with air, reconnected with the needle, and the needle's contents are blown onto a glass slide. Another slide is pressed to or drawn over the first to make a thin layer of cells. These slides are allowed to air-dry, although sometimes the pathologist will request additional alcohol-fixed or formalin-fixed smears to be prepared as well. A quick hematoxylin and eosin stain as used for traditional frozen section and a rapid, modified Wright-Giemsa stain* are made. Those stains can be ready for viewing in several minutes and, in the interest of speed, are used in preference to a Papanicolaou stain. While the hematoxylin and eosin stain gives the best cellular detail, the Wright-Giemsa stain provides metachromatic staining of stroma and mucin not well seen with the former. Cytological interpretation can be reported back to the surgeon within about ten minutes of the actual biopsy.

Results

Intraoperative fine needle aspiration was performed forty-one times in 35 patients: 39 lesions in 33 patients at thoracotomy and 2 lesions in 2 patients at mediastinoscopy (Table 1). Neoplastic cells were identified in each instance of tumor by needle aspiration. Of 30 malignant lesions, 23 had available histology. In 22 of those 23 malignant lesions (96%), the fine needle aspiration biopsy agreed with the final histological diagnosis regarding the presence of malignancy (Table 2), and in 16 of those 23

Table 1. Clinical Material for Intraoperative Fine Needle Aspiration Biopsy

	No. of Patients	No. of Lesions	Malignant	Benign
Thoracotomy	33[a]	39[a]	28	11
Lung lesion		28	18	10
Hilar or mediastinal lymph node		10	10	...
Mediastinal tumor		1	...	1
Mediastinoscopy	2	2	2	...
Total	35	41	30	11

[a]Six patients had aspiration of 2 different lesions.

Table 2. Results of Fine Needle Aspiration Biopsy in 30 Malignant Lesions in 24 Patients[a]

Operation	Result
Mediastinoscopy	2/2
Thoracotomy	
Lung lesion	17/18[b]
Hilar or mediastinal node	10/10

[a]Accuracy was 97%.

[b]Diagnostic error in 1 patient: breast metastasis misread as carcinoid.

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*"Diff-Quik," Harleco, 480 Democrat Rd, Gibbstown, NJ 08027.

Table 3. Correlation of Cytology of Intraoperative Fine Needle Aspiration in 23 Malignant Lesions with Available Histology

Final Histological Diagnosis	Cytological Diagnosis
LUNG LESIONS	
Squamous cell carcinoma—2	Squamous cell carcinoma—2
Adenocarcinoma—7	Adenocarcinoma—4 Carcinoma—3
Large cell undifferentiated carcinoma—1	Carcinoma—1
Oat cell carcinoma—2	Oat cell carcinoma—2
Mucoepidermoid carcinoma—1	Atypical cells—1
Metastatic endometrial carcinoma—2	Metastatic endometrial carcinoma—2
Metastic breast carcinoma—1[a]	Carcinoid—1[a]
LYMPH NODE LESIONS	
Adenocarcinoma—5	Adenocarcinoma—4 Carcinoma—1
Squamous cell carcinoma—1	Squamous cell carcinoma—1
Oat cell carcinoma—1	Oat cell carcinoma—1

[a]Diagnostic error in 1 patient.

Table 4. Results of Intraoperative Fine Needle Aspiration in 11 Benign Lesions

Final Surgical Diagnosis	Cytological Diagnosis at Operation
Granuloma—5 (Histoplasmoma in 2)	No tumor cells—2 Necrosis and inflammation—1 Amorphous debris—1 Granuloma—1
Hamartoma—3	No malignant cells—2 Possible hamartoma—1
Abscess—1	Necrosis and inflammation—1
Carcinoid tumor—1[a]	Lymphoma—1[a]
Dermoid cyst (mediastinum)—1	Squamous cells and hair shaft—1

[a]Diagnostic error in 1 patient.

(70%) the cytology report from the aspiration biopsy provided the correct neoplastic cell type as well as a diagnosis of malignancy (Table 3). Histology was not obtained from 7 lesions in patients with unresectable carcinoma because the definitive cancer diagnosis had been established by other means and diagnosis of the specific lesion by intraoperative fine needle aspiration was considered definitive. There was no false positive or false negative report for tumor as such. However, there was one false negative report for carcinoma. Two lesions misdiagnosed by fine needle aspiration were both problems of tumor classification: a metastatic breast carcinoma misdiagnosed as a carcinoid and a carcinoid misdiagnosed as lymphoma. Lobectomy was performed in each of those 2 patients. In no instance was a resection performed that, in light of the final histological diagnosis, was not indicated. With some granulomas, only necrotic debris was reported by intraoperative fine needle aspiration, but the lack of malignant cells was helpful in deciding that a limited resection should be performed (Table 4).

The overall diagnostic accuracy in identifying malignancy in our series was 95%. The technique was essentially complication free. In only 1 patient, a hematoma developed at the site of aspiration biopsy of a carcinoid tumor and was so noted in the resected lobectomy specimen.

The following two reports demonstrate the usefulness of intraoperative fine needle aspiration.

Patient 1

A 56-year-old female nurse was found on periodic routine health evaluation to have a new lung lesion on a chest roentgenogram (Fig 2). It was located in the anterior segment of the right upper lobe. Laminagraphy showed no signs of benignancy, and previous roentgenograms were available for comparison. She was a cigarette smoker and had a negative tuberculin test. Physical examination and standard laboratory workup were unremarkable. Sputum cytology findings were negative.

It was thought that exploratory thoracotomy was indicated. At operation a firm mass of 2 cm was palpated deep within the substance of the upper lobe. Wedge resection would have been impossible, and a segmental resection for diagnosis would have given a very narrow margin of resection at the anterior segmental bronchus, too close for tumor and sacrificing too much lung for benign disease. Intraoperative fine needle aspiration was performed. The report was "necrotic debris—no tumor seen" (Fig 3A). On the basis of that report, a local excision of the mass was performed, and barely any lung tissue was resected at the margins of the lesion. The histological diagnosis was a caseating *His-*

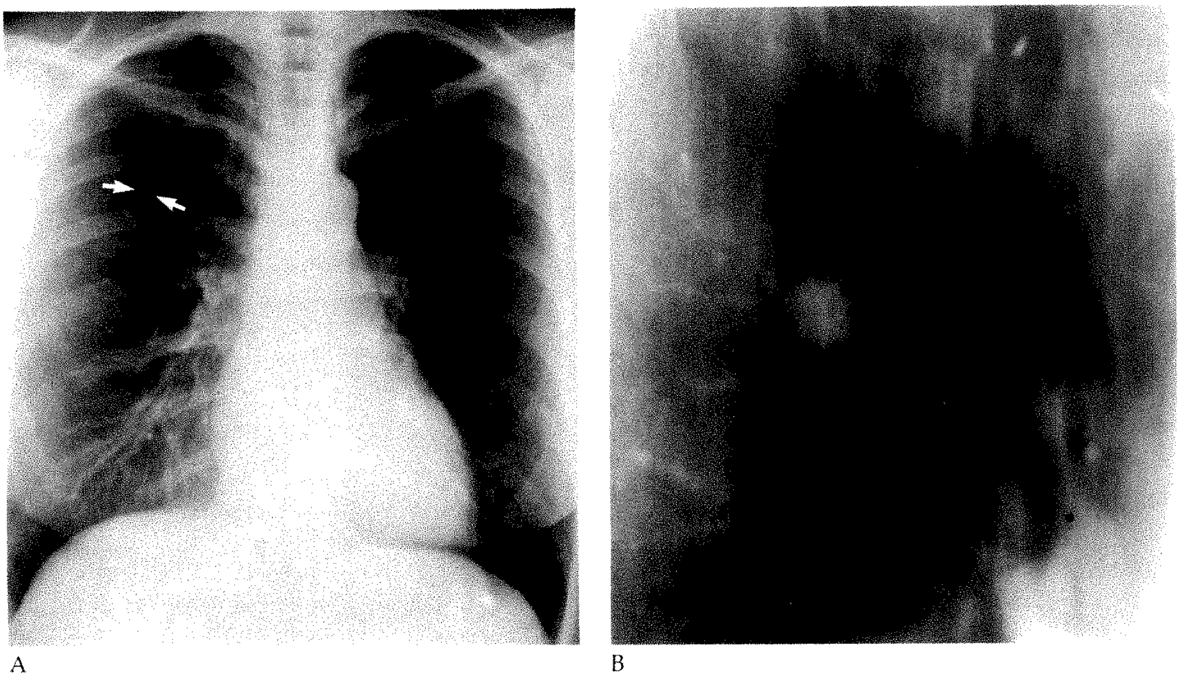

Fig 2. (Patient 1.) (A) Chest roentgenogram demonstrates a new lesion in the right upper lung field. (B) Laminagraphy of the lesion shows that it is in the anterior segment of the right upper lobe and contains no calcification.

toplasma granuloma (Fig 3B). The patient made an uneventful recovery.

COMMENT. Preoperative transthoracic needle biopsy was not performed because of the size and location of the lesion and because we thought that a 10% false negative rate for tumor diagnosis was not acceptable for a patient in such good general condition. Prior to our use of intraoperative fine needle aspiration, this patient would have undergone lobectomy with the sacrifice of a considerable amount of lung tissue.

Patient 2

A 58-year-old retired male police officer had an episode of hemoptysis. He was a smoker. Chest

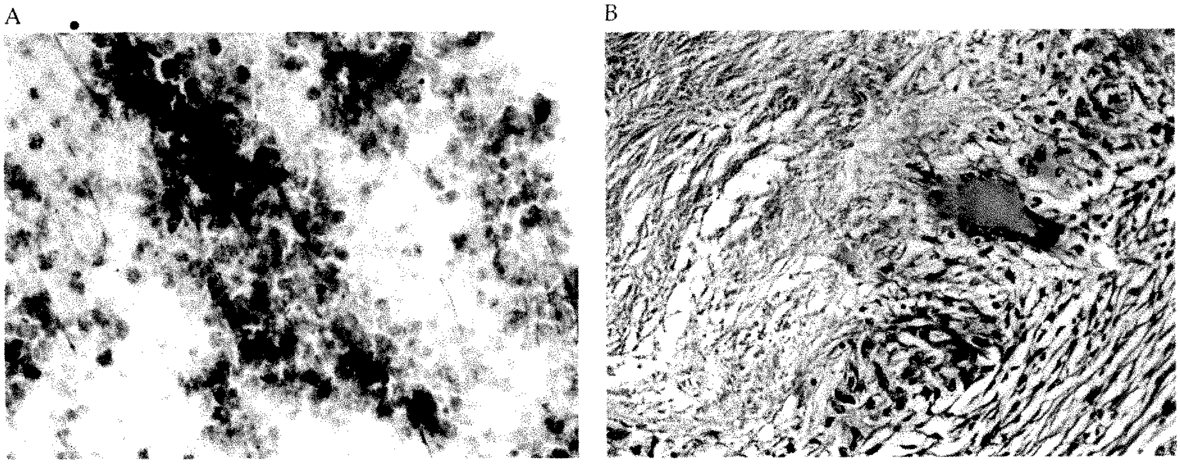

Fig 3. (Patient 1.) (A) Cytological study of intraoperative fine needle aspiration shows only necrotic debris. The failure to demonstrate tumor cells in such material has, in our experience, meant that there is no tumor present. (B) Photomicrograph of the resected specimen shows a typical granuloma. A few Histoplasma *organisms were identified on special stains. Cultures for fungi gave no growth. (A: Diff-Quik; B: H&E.)*

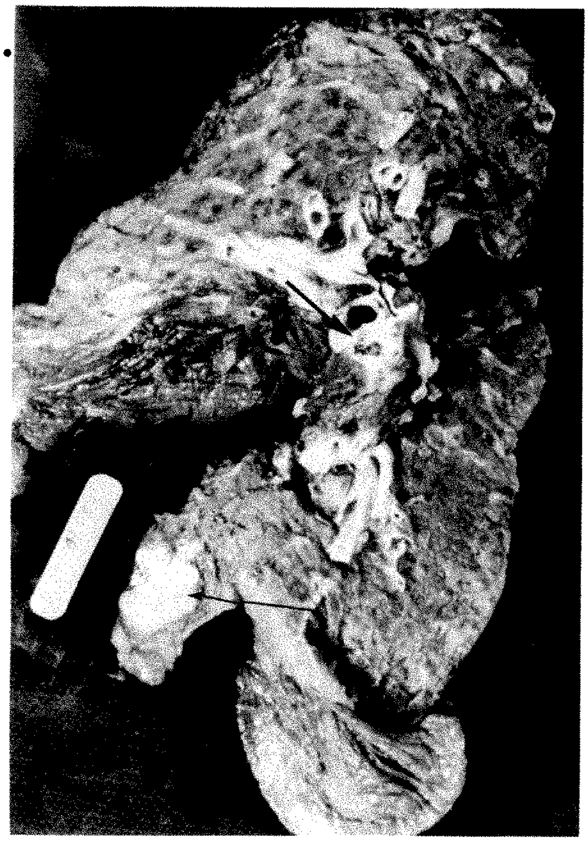

Fig 4. (Patient 2.) Sagittal section of the pneumonectomy specimen. The small arrow indicates the primary tumor. The large arrow indicates the metastatic tumor adherent to the pulmonary artery in the fissure. This tumor was biopsied by fine needle aspiration.

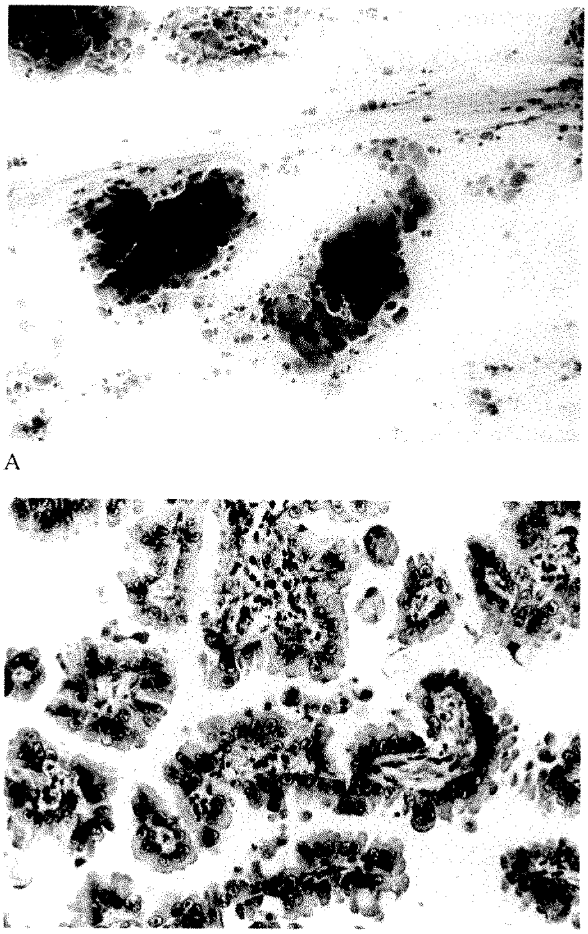

Fig 5. (Patient 2.) (A) Cytological preparation of the aspirated material from the lymph node in the fissure demonstrates adenocarcinoma. (B) Histological preparation from the same area of the pneumonectomy specimen shows how well the cytological and histological techniques correlate. (A: Diff-Quik; B: H&E.)

roentgenogram demonstrated a 3 cm mass in the left lower lobe. Flexible fiberoptic bronchoscopy with fluoroscopic control enabled biopsy of the mass, which was diagnosed as adenocarcinoma. Physical examination, routine blood and urine studies, and a workup for a primary tumor site other than the lung were all unremarkable.

At operation the lower lobe mass was obvious and not fixed. However, within the major fissure there was a firm mass adherent to the pulmonary artery, which, if tumor, would preclude a lobectomy (Fig 4). Fine needle aspiration of the mass was performed, and the aspiration cytology diagnosis was adenocarcinoma (Fig 5A). A left pneumonectomy was performed. The final histological diagnosis on the pneumonectomy specimen was "well differentiated peripheral adenocarcinoma of the lung with metastasis to lymph nodes in the fissure" (Fig 5B). The patient's postoperative recovery was satisfactory.

COMMENT. It is our practice to document by surgical pathology the specific indication for pneumonectomy. In this instance, although a small scalpel biopsy could have been taken and submitted for frozen tissue section, the lesion was adherent to the pulmonary artery in the fissure, and our experience with needle aspiration is that it is just as reliable but quicker and perhaps safer in such a situation.

Comment

Martin and Ellis [9] at Memorial Hospital in New York pioneered the use of needle aspiration biopsy in the evaluation of various neoplasms fifty years ago. The technique did not gain wide acceptance in the United States, however, until recent years, in spite of many reports from abroad [1, 11] documenting its safety, diagnostic accuracy, and technical ease. Recent reports in the literature indicate an increasing experience with fine needle aspiration biopsy in this country. Kline and Neal [7] reported an experience of 3,267 cases and a diagnostic accuracy rate of 90%. Other large series include those of Hajdu and Melamed [4] and Frable [3] who reported accuracy rates consistently over 80%.

The application of fine needle aspiration to lung lesions has received considerable recent attention and finally appears to have gained acceptance in the United States. Lalli and coworkers [8] reported 1,223 transthoracic needle aspiration biopsies with a diagnostic yield of 84%, and Sagel and colleagues [10] reported a positive diagnostic rate of 87% in 1,153 patients. Our own experience with transthoracic needle biopsy, spanning nine years and 181 patients, gave an accuracy rate of 84%.

The use of fine needle aspiration biopsy for rapid diagnosis in an operating room setting, in place of conventional frozen section, was described by Kline and colleagues [6] in a series of 28 pancreatic lesions diagnosed by this method at the time of celiotomy. They achieved a high degree of accuracy and encountered no complication. The practice of rapid staining and immediate reporting of cytological findings of needle aspirations of breast masses was reported by Duguid and co-workers [2] with favorable results. Those reports together with the known diagnostic accuracy of transthoracic needle biopsy led us to apply fine needle aspiration biopsy to thoracic lesions at the time of operation.

The results of our study indicate that intraoperative fine needle aspiration is a very valuable tool at thoracotomy for obtaining an initial diagnosis in exploratory cases and for determining whether or not lymph nodes are involved with tumor. It is particularly useful in diagnosing lesions deep within the lung parenchyma where its use can lead to conservative resection of benign lesions and confirm the appropriateness of resection for malignancy. It also appears to be highly accurate and safe at mediastinoscopy for biopsy of lesions in close proximity to major blood vessels. Ninety-six percent of the malignant lesions were diagnosed as such by this method, and 70% were even correctly diagnosed down to specific cell type.

The technique requires a cytopathologist experienced in fine needle aspiration biopsy [5], and that may be a limiting factor in some clinical settings. In competent hands, a cytological diagnosis based on fine needle aspiration is as definitive as a histological diagnosis based on frozen section. In summary, needle aspiration biopsy with immediate interpretation is a valuable addition to the operative diagnostic armamentarium of the surgeon.

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Carcinoma of the Lung: A Clinical Review

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ABSTRACT **Records of 702 patients with carcinoma of the lung seen from 1960 through 1970 were reviewed. The efficacy of various diagnostic and therapeutic procedures was assessed. Salient findings were as follows: Biopsy of *nonpalpable* ipsilateral supraclavicular lymph nodes was positive for carcinoma in 63 of 286 patients (22%). Even more surprising, biopsy of *nonpalpable* contralateral supraclavicular lymph nodes was positive for carcinoma in 9 of 38 patients (24%). Accordingly, the importance of biopsy of nonpalpable supraclavicular nodes is to be stressed. Squamous cell carcinoma was the most common type, but adenocarcinoma was more common in women and nonsmokers. Among the 702 patients, 48 (6.8%) were nonsmokers. The 5-year survival for 92 patients treated by lobectomy was 21%; the 5-year survival for 77 patients treated by pneumonectomy was 19%; the 5-year survival among 18 patients having resection of the chest wall in addition to resection of the primary lesion was 22%. Of 12 patients with small cell carcinoma of the lung treated by resection, there was 1 5-year survivor. The overall 5-year survival in the 702 patients was 6.6%.**

During an 11-year period, 702 patients were treated for carcinoma of the lung at two hospitals in Charleston, SC. Here we report our findings in these patients.

Material and Methods

From 1960 through 1970, 702 patients with carcinoma of the lung were treated at the Medical University Hospital and the Veterans Administration Hospital in Charleston. There were 416 white men (59.3%), 197 black men (28.0%), 59 white women (8.4%), and 30 black women (4.3%). The age distribution is shown in Table 1. Of the 702 patients, 558 were seen at the Medical University Hospital. There were 311 white men (55.7%), 158 black men (28.3%), 59 white women (10.6%), and 30 black women (5.4%). Among this group, the ratio of men to women was 5.27:1.

Of the 702 patients, 48 (6.8%) were known to not smoke tobacco. Smoking status was unknown in 190 patients. Of the remaining patients, 464 smoked cigarettes, 134 at least two packs per day, and 7 smoked cigars or pipes.

Nine major symptoms were noted among the 702 patients. The incidence was as follows: cough, 451 patients (64.2%); weight loss, 388 (55.3%): pain, 370 (52.7%); sputum, 312 (44.4%); hemoptysis, 199 (28.3%); malaise, 186 (26.5%); fever, 148 (21.1%); neuromyopathies, 68 (9.7%); and dizziness, 28 (4.0%). Some patients had more than one symptom. Although cough was the most frequent symptom, it was not necessarily the first one. Eighty-two patients (11.7%) were asymptomatic.

Abnormal physical signs varied depending on the presence or absence of complications such as atelectasis, pneumonia, pulmonary abscess, bronchial obstruction, pleural fluid, and chest wall involvement. Certainly, there were no characteristic signs, and in many there were no abnormal signs. Associated diseases included cardiovascular disease in 254 patients (36%), history of tuberculosis in 41 (6%), diabetes mellitus in 37 (5%), renal disease in 27 (4%), bronchiectasis in 17 (2%), and other malignancies in 40 (6%).

Cytological examination of the sputum was done in 489 patients. The results were positive in 188 patients (38%) and negative in 301 (62%). Bronchoscopy was performed in 503, and bronchial biopsy was positive in 230 (46%). Biopsies of the pleura by needle aspiration or limited thoracotomy in 46 patients were positive in 31 (67%). Pulmonary biopsies by needle aspira-

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Table 1. Age Distribution of 702 Patients with Carcinoma of the Lung

Age (yr)	No. of Patients	Percent
Under 40	16	2.3
40–49	107	15.2
50–59	257	36.6
60–69	201	28.6
70–79	109	15.5
80 and over	12	1.7
Total	702	100.0

Table 2. Results of Biopsy of Ipsilateral Supraclavicular Lymph Nodes of Patients with Carcinoma of the Lung

	Palpable (N = 118)			Nonpalpable (N = 541)		
Biopsy	No. of Patients	Percent	Result (%)	No. of Patients	Percent	Result (%)
Positive	64	54	70.3[a]	63	12	22.0[b]
Negative	27	23	29.7[a]	223	41	73.0[b]
Not done	18	15	. . .	233	43	. . .
Unknown	9	8	. . .	22	4	. . .

[a] Based on 91 patients with a result.
[b] Based on 286 patients with a result.

Table 3. Results of Biopsy of Contralateral Supraclavicular Lymph Nodes of Patients with Carcinoma of the Lung

	Palpable (N = 55)			Nonpalpable (N = 599)		
Biopsy	No. of Patients	Percent	Result (%)	No. of Patients	Percent	Result (%)
Positive	17	31	85.0[a]	9	1	23.7[b]
Negative	3	5	15.0[a]	29	5	76.3[b]
Not done	34	62	. . .	521	87	. . .
Unknown	1	2	. . .	40	7	. . .

[a] Based on 20 patients with a result.
[b] Based on 38 patients with a result.

tion or limited thoracotomy in 115 patients were positive in 104 (90%). Pleural fluid was evident on roentgenographic examination in 176 patients (25%). Cytological examination of the pleural fluid was done on one or more occasions in 77 patients and was positive in 32 (42%).

There was involvement of the left lung in 273 (38.9%) of the 702 patients and of the right lung in 397 (56.6%). Upper lobes were involved more often than lower. Both lungs were involved in 17 patients (2.4%). The involvement was not clear in 15 (2.1%). By clinical or roentgenographic examination or both, there was suspected spread of tumor to multiple sites. These sites included the hilar or mediastinal lymph nodes in 350 patients (50%), the chest wall in 97 (14%), the phrenic nerve in 40 (6%), the recurrent laryngeal nerve in 45 (6%), and the superior vena cava in 43 (6%). Some patients had two or more. All these sites were not proved, however.

Among 659 patients in whom it was recorded, palpable ipsilateral supraclavicular nodes were present in 118 patients. Biopsies were performed in 91; 64 (70%) had positive and 27 (30%) negative findings (Table 2). Five hundred forty-one patients had no palpable ipsilateral supraclavicular nodes. Biopsies were performed in 286 of them: in 63 (22%), the findings were positive for carcinoma and in 223 (78%), negative.

Among 654 patients in whom it was recorded, palpable contralateral supraclavicular nodes were found in 55 patients. Biopsies were done in 20: 17 (85%) had positive findings and 3 (15%), negative (Table 3). Contralateral supraclavicular nodes were not palpable in 599 patients. Biopsies in 38 of these 599 revealed that in 9 (24%) the findings were positive and in 29 (76%), negative.

The most common sites of proved metastases were as follows: lymph nodes, 232 (33%); bone, 126 (18%); brain, 94 (13%); contralateral lung (or separate primary), 72 (10%); liver, 57 (8%); and adrenal gland, 50 (7%). Some patients had multiple metastases, and many others had probable metastases in various sites.

Tumor Classification

A recent review of the pathological reports revealed that 170 of the patients had tumor types that were unclassified. Therefore, the microscopic slides of these 170 patients were studied again by one of us (J. S. M.), with a subsequent decrease in the number of unclassified cell types. The criteria utilized were, in general, those of the World Health Organiza-

Table 4. Tumor Classification in 702 Patients with Carcinoma of the Lung

Type	No. of Patients	Percent
Squamous cell	323	46
Adenocarcinoma	117	17
Large cell	71	10
Small cell	65	9
Bronchioloalveolar	9	1
Other or unclassified	117	17
Total	702	100

Table 5. Tumor Classification by Sex in 702 Patients with Carcinoma of the Lung

	Men		Women	
Type	No. of Patients	Percent	No. of Patients	Percent
Squamous cell	298	48.6	25	28
Adenocarcinoma	85	13.9	32	36
Large cell	59	9.6	12	13.5
Small cell	60	9.8	5	6
Bronchioloalveolar	6	1	3	3
Other or unclassified	105	17.1	12	13.5
Total	613	100	89	100

tion. The diagnosis of squamous cell (epidermoid) carcinoma was made only if either intracellular bridges (prickles) or evidence of keratin production was seen. The diagnosis of adenocarcinoma required either gland or tubule formation or intracytoplasmic mucin. When the tumor appeared to originate peripherally and when the neoplastic cells grew along the alveolar walls, the diagnosis of bronchioloalveolar carcinoma was made. When there were no clearly defined differentiating features, the diagnosis was undifferentiated carcinoma. These lesions were further divided into two categories: large cell and small cell. No further attempt was made to subclassify the neoplasms. In all other instances, the tumors were classified as other or unclassified. Cases of carcinoid were excluded from the study. The resultant cell types are shown in Table 4. It is of note that although squamous cell carcinoma was the most common, adenocarcinoma was more common in women and nonsmokers (Tables 5, 6).

Table 6. Relationship of Histological Type to Smoking History of 512 Patients with Carcinoma of the Lung

	464 Smokers		48 Nonsmokers	
Type	No. of Patients	Percent	No. of Patients	Percent
Squamous cell	220	47.4	14	29.2
Adenocarcinoma	65	14.0	18	37.5
Large cell	47	10.1	6	12.5
Small cell	51	11.0	2	4.2
Bronchioloalveolar	6	1.3		
Other or unclassified	75	16.1	8	16.7

Fifty-six (8%) patients had cavitary lesions on roentgenographic examination. Cell types for the cavitary lesions were as follows: squamous cell, 40 (71%); large cell, 6 (11%); adenocarcinoma, 5 (9%); bronchioloalveolar, 1 (2%); small cell, 0; and other, 4 (7%). Three (5%) of the 56 survived longer than 5 years.

Operative Intervention

Of the 702 patients studied, 278 had a standard posterolateral thoracotomy (operability rate, 40%). The mean time from the onset of symptoms until operation was 6.2 months. The operations performed were as follows: exploration only, 41 (diagnosis had been established previously); biopsy only, 46; wedge resection only, 3; lobectomy (or bilobectomy on right), 92; pneumonectomy, 77; pulmonary resection with chest wall resection, 18 (12 with lobectomy, 6 with pneumonectomy); and resection of carina, 1.

Results

There were several complications associated with operation. These included pneumothorax (21 patients or 7.5%); pneumonia (15 or 5%); bronchopleural fistula (15 or 5%); bleeding (12 or 4%); and wound infection (11 or 4%). An empyema developed in 11 patients (6%) among 187 having lobectomy or pneumonectomy.

Ninety patients underwent only exploration, biopsy of tumor, or wedge resection. Of these patients, only 1 who had had wedge resection survived more than 5 years. Of the 104 patients who had a lobectomy (including 12 who had

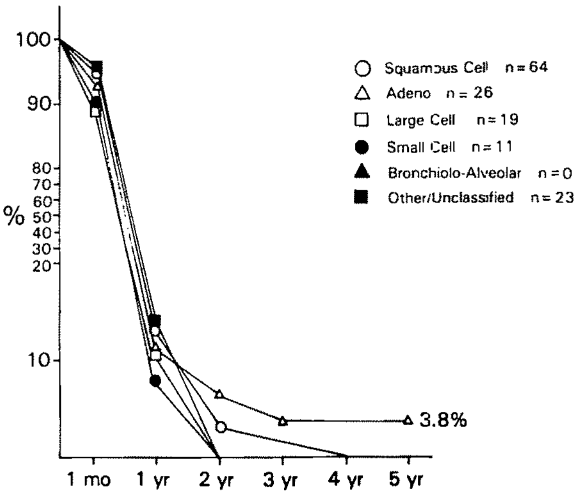

Fig 1. Survival by cell type for patients with carcinoma of the lung with *cervical lymph node metastases.*

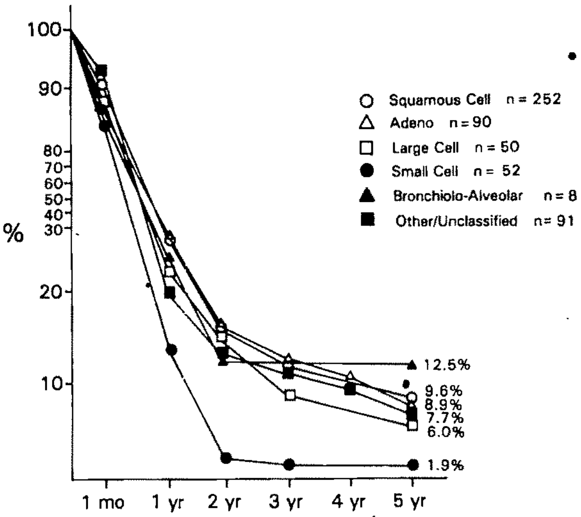

Fig 2. Survival by cell type for patients with carcinoma of the lung without *cervical lymph node metastases.*

concomitant chest wall resection), 5 died (mortality, 4.8%) and 23 (22%) survived 5 years or longer. Of the 83 patients who had a pneumonectomy (including 6 having concomitant chest wall resection), 5 died (mortality, 6.0%) and 16 (19%) survived 5 years or longer. Of the 18 patients who had chest wall resection, 4 (22%) survived longer than 5 years. The patient who had resection of the carina died in less than thirty days. It may be worthy of note that 3 (25%) of 12 patients having lobectomy after receiving preoperative irradiation survived 5 years or longer and that 5 (24%) of 21 patients having pneumonectomy after preoperative irradiation survived more than 5 years. The total number of rads administered to 7 of 8 of the long-term survivors ranged from 2,750 to 4,000 (average, 3,312). In the remaining patient, 3,500 rads was given over a left temporal lobe metastasis and none over the primary in the lung. Immediate or delayed postoperative irradiation was followed by a 5-year survival of 8% (3 out of 36) for lobectomy and 9.5% (2 out of 21) for pneumonectomy. Radiotherapy alone was administered to 304 patients, 3 of whom (1%) lived longer than 5 years. Chemotherapy as an adjunct to radiation therapy in 32 patients resulted in no 5-year survivors. Chemotherapy alone in 26 patients resulted in no survivors past a year.

Regardless of the method of treatment, if any, the survival for the different cell types, with and without supraclavicular lymph node metastasis, is shown in Figures 1 and 2. Of 250 patients with negative ipsilateral supraclavicular node biopsies, 15 (6%) survived longer than 5 years compared with 4 (3%) of the 127 patients with positive biopsies. Of 32 patients with negative contralateral supraclavicular biopsies, 4 (12.5%) survived longer than 5 years. Of 26 patients with positive contralateral supraclavicular node biopsies, none survived longer than 5 years.

Comments

The age and sex distributions in our series are in rough agreement with a number of previous series [3, 7, 10, 21, 22]. Sex and race had no important bearing on survival in this study. The study also affirmed the already established fact that most patients with carcinoma of the lung have been tobacco smokers [3]. The etiology is still unknown [8].

Of the diagnostic studies performed, the simplest, sputum cytology, was diagnostic in 38% of our patients. Of the 503 who underwent bronchoscopy, diagnosis was established by bronchial biopsy in 46%; this was before the flexible bronchoscope and transbronchial biopsy were available. In patients with pleural fluid, cytological examination of the fluid was shown to be a valuable diagnostic test in that 32

(42%) of the 77 studied had positive results. The presence of pleural fluid was an ominous prognostic sign: only 1 of 45 who had a negative cytological examination survived more than 5 years. No patients with positive pleural fluid cytological examination survived for 5 years.

The presence of cavitation had no influence on survival in our patients since the 5% 5-year survival of patients with cavitation is comparable with 5% (27 out of 521) of patients without cavitary lesions (excluding 125 patients in whom the presence or absence of cavitation was not recorded). It was noted by Mittman and Bruderman [12] that cavitary carcinomas usually are squamous cell and seldom oat cell. None of our 56 patients with cavitary lesions had small cell carcinoma.

The most common sites of metastases in order of frequency were lymph nodes, bone, brain, contralateral lung, liver, and adrenal glands. No evaluation of routine isotopic scans was made in this review, but Ramsdell and co-workers [15] evaluated 100 patients with lung carcinoma (excluding oat cell) by routine liver, brain, and bone scans. Of 131 scans performed on patients with no clinical evidence of involvement, only 1 was a correct positive. Conversely, of 17 positive scans in these patients, 16 were false positives.

Biopsy was diagnostic in 70% (64 out of 91) of the patients with palpable ipsilateral supraclavicular nodes and in 85% (17 out of 20) of the patients with palpable contralateral supraclavicular nodes (see Tables 2, 3). The practice of supraclavicular node biopsy in the absence of palpable nodes has been questioned by many surgeons [2, 4, 23], but in this study positive nodes were found in 22% (63 out of 286) of the patients with nonpalpable ipsilateral nodes and in 24% (9 out of 38) of patients with nonpalpable contralateral nodes. These results are similar to those of Brantigan and colleagues [5] who evaluated 341 consecutive patients with carcinoma of the lung by bilateral supraclavicular node biopsies. Positive biopsies were found in 68 (23.8%) of 286 patients with nonpalpable nodes [5]. In light of the ease and safety of this procedure, which can be performed under local anesthesia, it should be performed routinely in patients with nonpalpable nodes for accurate staging before deciding on the optimal methods of treatment.

Mediastinoscopy was not evaluated in this review, but it has been shown to be a valuable and safe method for both diagnosis and determination of resectability [8, 9, 14, 19].

It has been reported that postoperative empyema may prolong survival after resection for carcinoma of the lung [16, 18]. This was not the case with our 11 patients in whom an empyema developed after lobectomy or pneumonectomy, with or without concomitant chest wall resection. Only 1 survived longer than 5 years.

Preoperative irradiation apparently did not have an adverse effect on survival of patients undergoing resection; 24% of those undergoing pneumonectomy and 25% of those having lobectomy survived more than 5 years. This survival after resection following preoperative irradiation is contradictory to the results of Baker and co-workers [1] who followed 17 patients with no tumors found in the surgical specimen after irradiation with cobalt 60. All but 1 were dead at the time of follow-up. Shields [17] evaluated 331 patients with biopsy-proved bronchial carcinoma in a randomized study in which one group received preoperative irradiation and resection, and the other group resection only. He found no advantage in preoperative irradiation and probable harmful effects on survival at 4 years.

The patients requiring chest wall resection had a reasonable survival with 21% (4 out of 19) living more than 5 years. Geha and associates [6] reported that 12 out of 41 patients (29%) survived 5 years after en bloc excision of the chest wall for curative resection with and without postoperative irradiation. For superior sulcus carcinoma, Paulson and Urschel [13] reported survival longer than 5 years for 16 out of 46 (35%) patients who underwent preoperative irradiation combined with extended resection. These results support the thesis that chest wall involvement is not a contraindication to resection of pulmonary carcinoma if the chest wall involvement is a direct extension and not a distant metastasis.

In agreement with previous series [10, 20, 21], the most frequent cell type among our patients was squamous (46%) and the second, adenocarcinoma (17%). Many physicians believe that the pathological finding of small cell carcinoma of the lung is a contraindication to resection. Jones and colleagues [10] reported no 5-year survivors among 21 patients who underwent resection of oat cell carcinoma, and Miller and co-workers [11] found superior survival with radiotherapy compared with resection for oat cell carcinoma. In our study, patients with small cell carcinoma who underwent thoracotomy and resection had a 5-year survival of 8% (1 of 12). The overall 5-year survival for the entire 702 patients was 6.6%.

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Clinical Spectrum of Pulmonary Hamartomas

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ABSTRACT **Pulmonary hamartomas are tumors that occur in the parenchyma or the bronchi. Though the lesions themselves are benign, they may be associated with malignant neoplasms or they may cause obstruction of the bronchi because of their location. Pulmonary hamartomas were resected in 29 patients at the Ochsner Medical Institutions during a 30-year period. Of these patients, 6 had symptoms related to concomitant malignancy and 3 had symptoms resulting from obstruction of the bronchi by the hamartoma.**

Surgical treatment ranged from enucleation to pneumonectomy. One patient died in the hospital of extensive bronchogenic carcinoma. In 2 others, carcinoma of the lung developed within twelve months after resection of a hamartoma.

In this group of patients, 20% had concomitant or subsequent pulmonary lesions. Ten percent of the hamartomas were located in the bronchi, resulting in bronchial obstruction. A surgical approach is indicated for lesions that appear to be pulmonary hamartomas on roentgenograms.

The term *hamartoma* was introduced by Albrecht [1] in 1904 to designate lesions composed of elements of tissue that are native to an organ but are present in a disorganized array. Pulmonary hamartomas are benign tumors that occur in the lungs or the bronchi. Clinical interest in pulmonary hamartomas centers around two problems: (1) differentiating them from malignant lesions and (2) recognizing them as the cause of secondary symptons, such as atelectasis with infection resulting from the tumor's location.

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Material and Methods

Between August, 1949, and December, 1978, at the Ochsner Medical Institutions, 29 pulmonary hamartomas were resected, accounting for 0.01% of all pulmonary resections done during that time. The 17 male and 12 female patients ranged from 4 to 75 years old. Follow-up was possible in all patients and ranged from less than 1 year to 19 years.

Twenty of the 29 patients had no symptoms. Recurrent pneumonia was the predominant symptom in the remaining 9 patients. The symptoms were as follows: pneumonia, 4 patients; hemoptysis, 2; dyspnea, 2; obstruction of the superior vena cava, 2; and chest pain, 3.

Findings on chest roentgenograms of all patients were abnormal. Twenty-one patients had solitary nodules, with calcification in 5 (17%) of the tumors. Four patients had other associated lesions. In the remaining 4 patients, findings were consistent with pneumonia, atelectasis, or abscess. Bronchography revealed bronchial obstruction in 2 patients.

The lesions were located in the pulmonary parenchyma in 26 of the 29 patients (90%) and in a major bronchus of each of 3 patients. The distribution of the lesions was as follows: right upper lobe, 9 lesions and left upper lobe, 5; right middle lobe, 3 and left middle lobe, 3; and right lower lobe, 8 and left lower lobe, 1. There was a total of 20 lesions on the right and 9 on the left.

Bronchoscopy was done in 26 of 29 patients. Although 2 of the 3 endobronchial lesions were seen, biopsies of them were not diagnostic.

Surgical procedures consisted of enucleation or wedge resection for small peripheral lesions (20 patients), lobectomy (8 patients), and pneumonectomy (1 patient). No patient was a candidate for sleeve resection. Aggressive procedures were necessary when concomitant malignancies were encountered.

The patient who underwent radical intrapericardial pneumonectomy for concurrent

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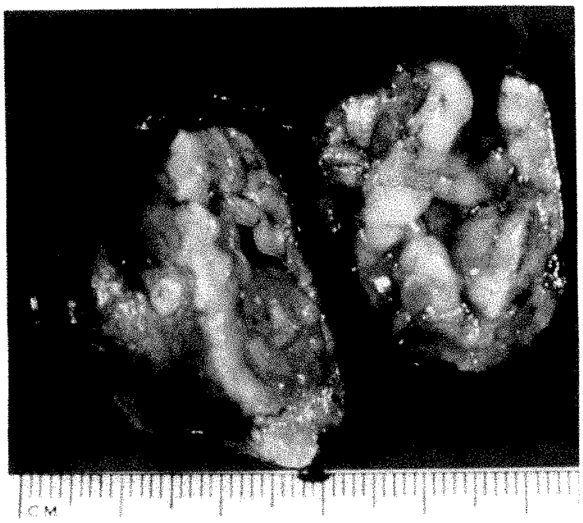


Fig 1. Typical appearance of pulmonary hamartoma.

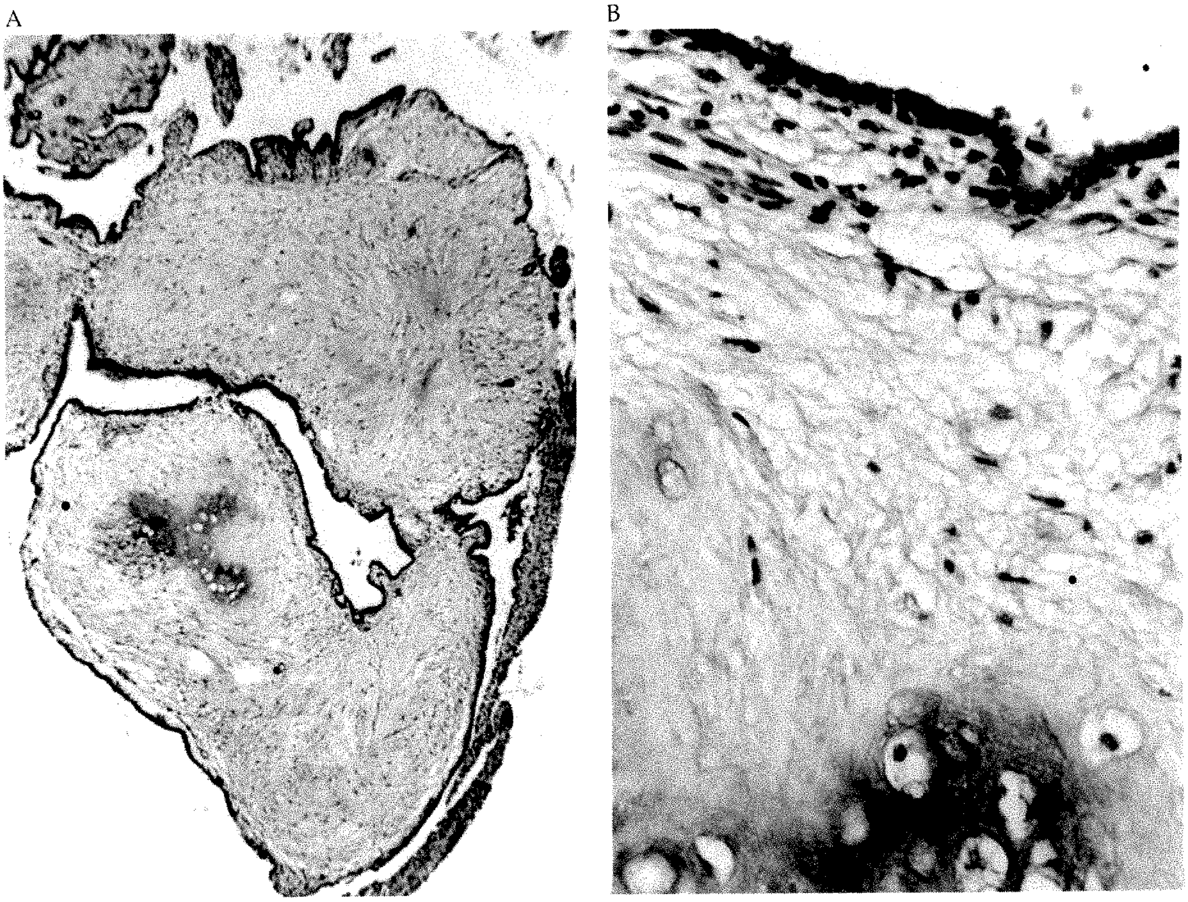
pulmonary carcinoma died in the hospital. Four patients died late of pulmonary malignancies. No evidence of recurrence has been found in the remaining 24 patients.

Comment

Pulmonary hamartomas are the most common benign tumors of the lung, accounting for about 8% of pulmonary lesions [8]. The presence of a pulmonary hamartoma is usually of interest to the internist, lung specialist, and thoracic surgeon only insofar as it must be differentiated from a malignant process. Occasionally, however, this benign lesion may cause important symptoms because of its location [4, 12–14].

Whether pulmonary hamartomas are acquired or developmental in origin is a matter of debate [7]. McDonald and co-workers [9] reported that a developmental error from misplaced bronchial analogues accounted for the development of pleural hamartomas. Bateson [2], on the other hand, considers them to be

Fig 2. (A) Note septa of connective tissue and glandlike formation. (B) Cuboidal cells line glandlike formations. (A: H&E; ×45 before 31% reduction.) (B: H&E; ×320 before 31% reduction.)



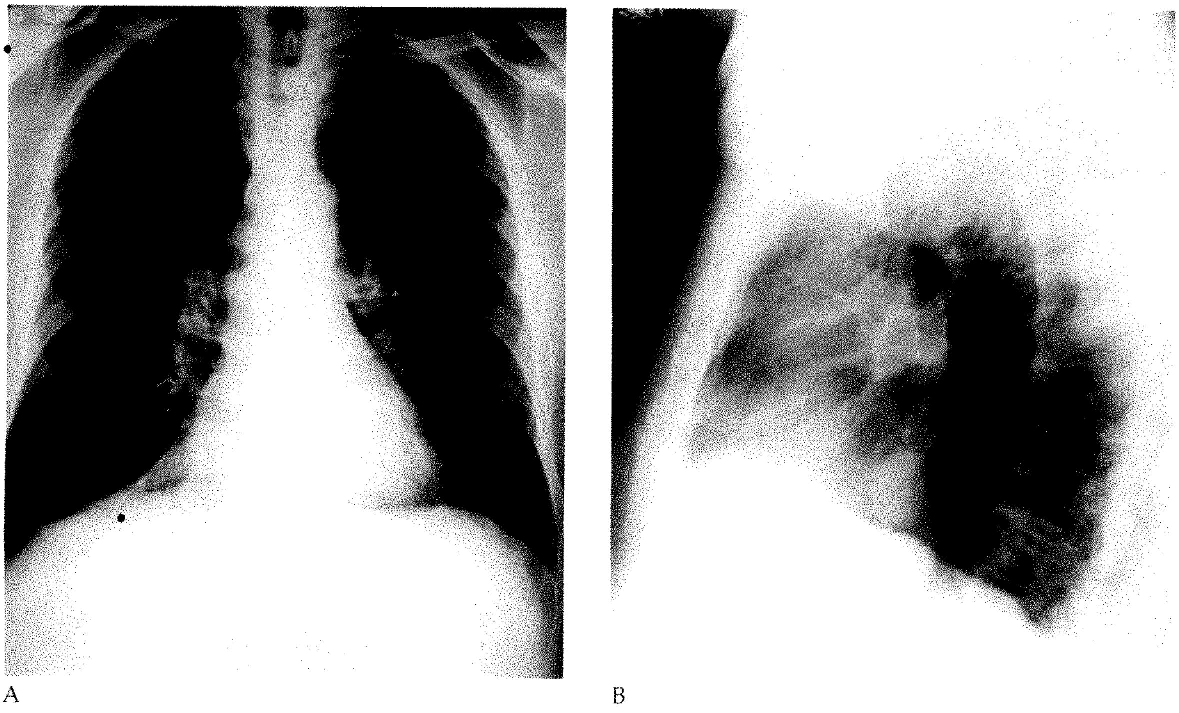


Fig 3. (A) Posteroanterior and (B) lateral roentgenograms demonstrating a rather large, benign-appearing lesion.

true neoplasms. His idea is based on demonstration of slow growth and onset of hamartomas in older groups.

Four stages of growth were described by Ober and Kaiser [11]: (1) displacement, (2) normally controlled growth, (3) mildly accelerated growth, and (4) rapidly accelerated growth. Usually pulmonary hamartomas are found in the pulmonary parenchyma, but approximately 10% occur in the bronchial lumen [6]. The tumors range in size from 1 to 30 cm. On gross examination, their surfaces appear lobulated and smooth with small areas of cartilage (Fig 1).

The nodules are composed mainly of cartilage. Deep septa of connective tissue extend from the periphery to the center (Fig 2A). Glandlike formations lined with cuboidal cells are also present (Fig 2B) [3]. There is no capsule or invasion into surrounding lung tissue. More detailed description of the ultrastructure and theories of formation are available [2, 15].

Findings on chest roentgenogram vary according to the size and location of the tumor. The contour is usually lobular with a smooth surface, as seen in Figure 3. However, some lesions may be slightly irregular and more nearly mimic a malignant lesion. Stippled or popcornlike calcification is seen in about 10% of pulmonary hamartomas. Endobronchial lesions may not be visible themselves, but the results of bronchial obstruction they cause, such as atelectasis, pneumonia, or even abcess (Fig 4), usually are. Occasionally bronchography has been helpful in identifying bronchial obstruction.

Twenty of the patients in this series were considered to be asymptomatic. Four patients had pneumonia; 2, hemoptysis; 2, dyspnea; 2, obstruction of the superior vena cava; and 3, chest pain. In only 3 of these patients were symptoms thought to be secondary to the hamartoma. In the remaining patients they were attributed to diffuse parenchymal pulmonary disease (2), a malignant pulmonary lesion (1), or an unknown cause (2). In the 3 patients with symptoms directly referable to a hamartoma, the lesions were endobronchial. One lesion occurred in the right lower lobe, 1 in the right middle lobe, and the third in the left upper lobe. All 3 patients had symptoms and clinical findings of pneumonia. Reports from other centers seem to verify the fact that

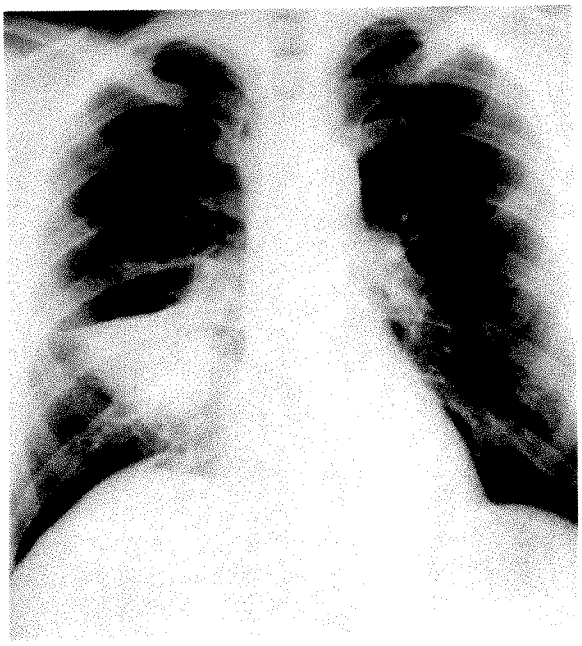


Fig 4. Pneumonia secondary to obstruction caused by endobronchial hamartoma. Tomography also revealed an abscess.

symptoms are secondary to atelectasis, infection, and tissue destruction distal to the intraluminal lesion [4, 10, 12, 13].

The ages of these 3 patients were 4, 39, and 45 years. The youngest previously reported patient with an endobronchial hamartoma was 16 years old. Butler and Kleinerman [5] commented in 1969 on the fact that the disease had not at that time been reported in children. Indeed, most patients with intraparenchymal tumors are in the fifth and sixth decades of life. Endobronchial location in the group of 29 patients was slightly less than 10%. In previous reports the incidence of endobronchially located lesions compared with parenchymally located lesions was 3 to 20%.

Histology of the endobronchial and parenchymal tumors was essentially the same. There were no signs of invasion or malignant differentiation in any of the tumors resected. Bronchoscopy identified 2 endobronchial tumors; however, biopsy did not yield a diagnosis. Lobectomy was carried out in all 3 patients with endobronchial lesions. All had an uneventful recovery, and there has been no sign of recurrence.

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Intraoperative Trauma to Human Saphenous Veins: Scanning Electron Microscopic Comparison of Preparation Techniques

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ABSTRACT **To determine optimal preparation techniques for human saphenous veins, a scanning electron microscopic comparison was made of the effects of variations in solutions, temperatures, and distention pressures on human vein morphology. Segments of saphenous veins obtained from 20 patients undergoing myocardial revascularization were divided into five groups of 5 veins each.**

Group 1 segments (controls) were immediately distended and perfusion-fixed with glutaraldehyde at 30 mm Hg to simulate in vivo saphenous vein hydrostatic pressure. Segments comprising Groups 2 and 3 were placed in heparinized normal saline solution at 28°C for one hour and then distended to either 100 mm Hg (Group 2) or 300 mm Hg (Group 3). Segments making up Groups 4 and 5 were immersed in heparinized blood for one hour at either 28°C (Group 4) or 4°C (Group 5), and then distended to 100 mm Hg. Except for controls, which were fixed as described, all other groups of vein specimens were perfusion-fixed at 100 mm Hg to simulate in vivo arterial pressure.

Control veins showed focal intimal fractures with minimal endothelial cell loss due to harvesting manipulation. Groups 2 and 3 had marked endothelial loss, which led to exposure of basement membrane, collagen fibrils, and smooth muscle cells and was associated with intimal and medial edema. Veins prepared with blood appeared similar to controls, showing focal endothelial cell loss, but preservation of intimal and medial structure. Changes were less marked in Group 5 than in Group 4. We conclude that human saphenous veins are best preserved by immersion in cold blood and distention to a pressure of 100 mm Hg or less.

Aortocoronary bypass grafts using autogenous saphenous veins are subject to early and late occlusion. Problems related to operative technique, distal coronary artery runoff, hyperlipidemia, graft ischemia, and vein preparation techniques have been implicated as causes of bypass graft failure [2, 5, 9, 13, 25, 26]. Although investigations in animals suggest that vein immersion in saline solution and vein distention above physiological pressures cause vein endothelial cell and mural damage [1, 6, 13, 20, 22, 25], no systematic evaluations of these problems have been performed using human saphenous veins [2, 3, 6, 7, 13, 22, 28]. To determine preferable techniques for preserving vein integrity, we compared human graft preparation techniques, evaluating the veins by scanning electron microscopy.

Materials and Methods

Portions of saphenous veins from 20 patients undergoing coronary artery bypass operations were divided in 25 segments, each measuring 4 to 5 cm in length. These segments were divided into five groups of 5 veins each. Segments from Group 1 (control) were immediately fixed by perfusion with cold, buffered (pH 7.2) 3% glutaraldehyde at 30 mm Hg distention pressure, using a constant pressure perfusion device (Fig 1) to approximate the in vivo hydrostatic venous pressure in the standing position. Group 2 veins were immersed in heparinized normal saline solution (0.9% sodium chloride) at 28°C for one hour and then distended to a pressure of 100 mm Hg with normal saline solution. Group 3 veins were immersed in heparinized normal saline solution at 28°C for one hour, followed by distention to a pressure

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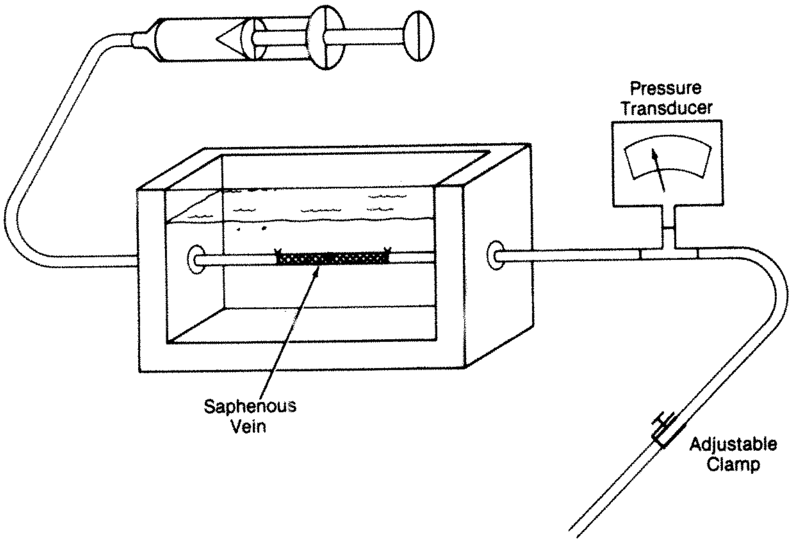

Fig 1. Constant pressure perfusion device, which allows perfusion and fixation of a saphenous vein in various solutions at constant distention pressure.

of 300 mm Hg. Group 4 veins were immersed in heparinized arterial blood at 28°C for one hour and afterward distended to a pressure of 100 mm Hg with autologous human blood. Group 5 veins were immersed in heparinized arterial blood at 4°C for one hour and then distended with blood to a pressure of 100 mm Hg. After pressure distention, all groups of veins, except for controls, were fixed with cold, buffered (pH 7.2) 3% glutaraldehyde at a perfusion pressure of 100 mm Hg, simulating human in vivo arterial pressure.

After fixation, the vein segments were divided in half longitudinally. From each, two 0.5 cm sections were prepared for scanning electron microscopy by critical-point drying and coating with gold-palladium. Each half of the vein segment was examined for pathological damage both en face and in cross section in a JEOL 35C scanning electron microscope. The types of pathological damage observed included endothelial cell separation, endothelial cell loss, exposed basement membrane, exposed fibrillar collagen, intimal edema, medial edema, and intimal and transmural vein fractures. These types of pathological damage were graded on a scale of 0 to 4 on the basis of percent involvement of the vein segment: 0 = no damage; 1 = less than 10%; 2 = 10 to 25%; 3 = 25 to 50%; and 4 = more than 50%. We utilized the sum of these grades for each of the pathological alterations in each of the five groups of vein segments as a numerical representation of the total amount of vein trauma produced by each of the five techniques for preparation of vein grafts (Table).

Results

All vein segments in Group 1 (control) demonstrated occasional endothelial cell separation and endothelial cell loss with minimal exposure of fibrillar collagen or basement membrane (Fig 2). These specimens showed fractures, with clefts extending through the intima and into the media. We presume that these fractures occur from manipulation during operation because veins in all groups showed similar intimal fractures. Group 1 veins had no separation of the intima from the media and no edema (Fig 3A). The total pathological damage score for Group 1 was 4, the lowest score for all groups studied.

All veins in Group 2 (28°C saline solution, 100 mm Hg) had marked, grade 4, endothelial cell separation and grade 3 endothelial cell loss, exposing large amounts of basement membrane and fibrillar collagen (Fig 4A). Intimal fractures occurred more frequently than in control veins and separation of the intima from the media occurred in 3 specimens (Fig 3B). Edema was present in all specimens in this group. The total

Damage Scores in Five Groups of Vein Segments[a]

Group (5 veins each)	Endothelial Cell Separation	Endothelial Cell Loss	Exposed Basement Membrane	Exposed Collagen	Intimal Edema	Medial Edema	Intimal Fractures	Total Damage Score
Group 1 Control 30 mm Hg	1	1	0	0	0	0	2	4
Group 2 NSS storage 28°C 1 hr 100 mm Hg	4	3	2	2	2	2	3	18
Group 3 NSS storage 28°C 1 hr 300 mm Hg	4	4	3	2	4	4	3	24
Group 4 WB storage 28°C 1 hr 100 mm Hg	2	2	2	1	1	1	2	11
Group 5 WB storage 4°C 1 hr 100 mm Hg	2	1	1	1	0	0	2	7

[a]Damage score: 0 = no change; 1 = occasionally observed; 2 = 10 to 25% of vein involved; 3 = 30 to 50% of vein involved; 4 = more than 50% of vein involved.

NSS = normal saline solution; WB = whole blood.

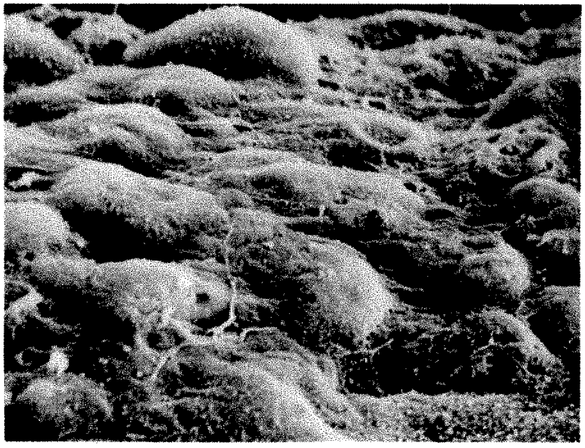

Fig 2. Endothelial surface of Group 1 vein (control) shows good preservation of endothelial cells with intact intercellular connections. Bulging nuclei and surface microvilli are seen clearly. (×1,300 before 40% reduction.)

pathological damage score for Group 2 vein segments was 18.

Veins in Group 3 (28°C saline solution, 300 mm Hg) showed grade 4 endothelial cell separation and endothelial cell loss, exposing large areas of basement membrane (Fig 4B). Intimal fractures were more pronounced than in control veins. The wall thickness was decreased, with separation of the intima from the media (Fig 3C). Edema was present between smooth muscle fibers. This group showed more damage than any of the others, having a damage score of 24.

Veins in Group 4 (28°C blood, 100 mm Hg) demonstrated endothelial cell separation and endothelial cell loss involving 10 to 25% of the intimal surface. The remaining intima appeared identical to that of control veins. Grade 2 areas of exposed basement membrane occurred while fibrillar collagen was exposed only occasionally (Fig 5A). There was minimal intimal or medial edema. The total damage score for Group 4 was 11.

Veins in Group 5 (4°C blood, 100 mm Hg) had mild endothelial cell separation with endothelial cell loss similar to that of control veins. Fibrillar collagen and basement membrane were only occasionally exposed (Fig 5B). Fractures appeared in numbers similar to control veins. There was no intimal or medial edema (Fig 3D). The total damage score for Group 5 was 7, similar to that of Group 1.

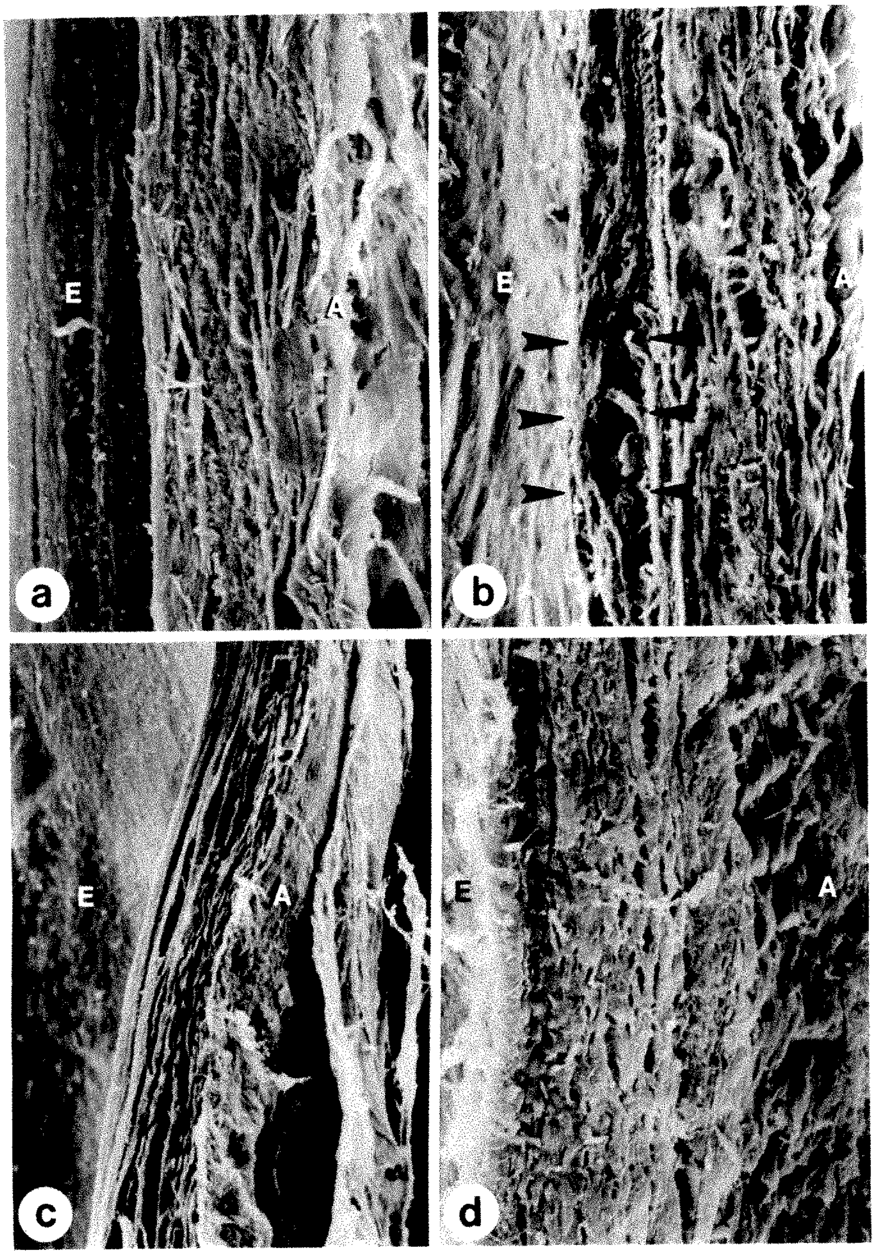

Fig 3. Low-power views of scanning electron micrographs of vein walls. Endothelial surface (E) *is shown on the left and the adventitial surface* (A) *on the right. (A) Cross section of Group 1 vein (control) shows endothelial surface and adventitial surface. Edema in the wall is absent. (×150 before 10% reduction.) (B) Cross section of Group 2 vein (saline immersion) shows separation of intima* (arrowheads) *from media. Areas of muscle fiber separation in media represent edema. (×130 before 10% reduction.) (C) Cross section of Group 3 vein (saline immersion with 300 mm Hg distention) shows fine separation of intima from media and marked fiber separation in media, representing severe edema. (×94 before 10% reduction.) (D) Cross section of vein immersed in cold blood (Group 5) is representative of blood-immersed veins. The appearance is compact, similar to that of a control vein, with no intimal-medial separation and minimal separation of medial fibers. (×540 before 10% reduction.)*

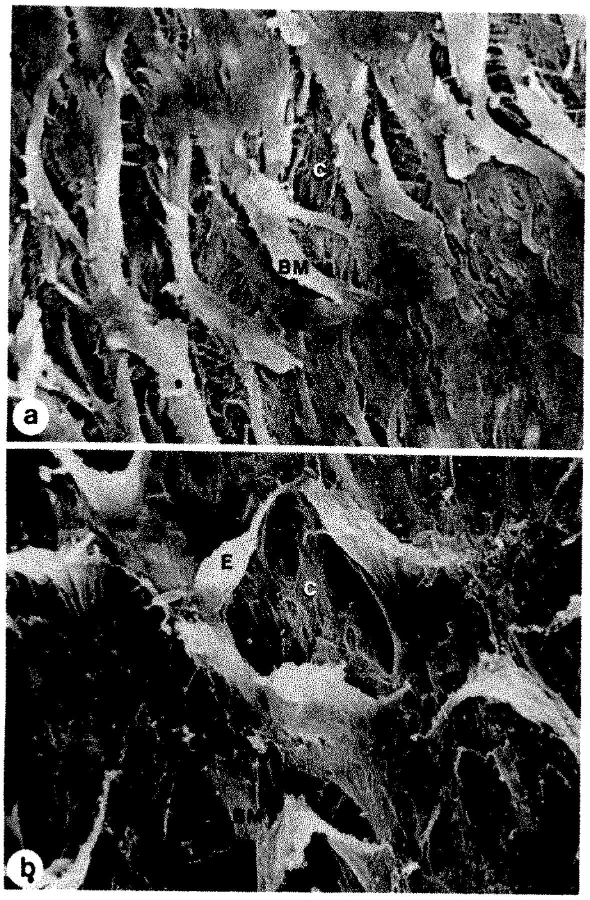

Fig 4. (A) Endothelial surface of saline-immersed vein (Group 2) shows an area of total endothelial cell loss, with exposed basement membrane (BM) *and fibrillar collagen* (C). *(×720 before 40% reduction.) (B) Endothelial surface of saline-immersed vein distended with 300 mm Hg pressure (Group 3) shows typical rolled-up appearance of separated endothelial cells* (E), *beneath which exposed basement membrane and collagen are seen. (×1,600 before 40% reduction.)*

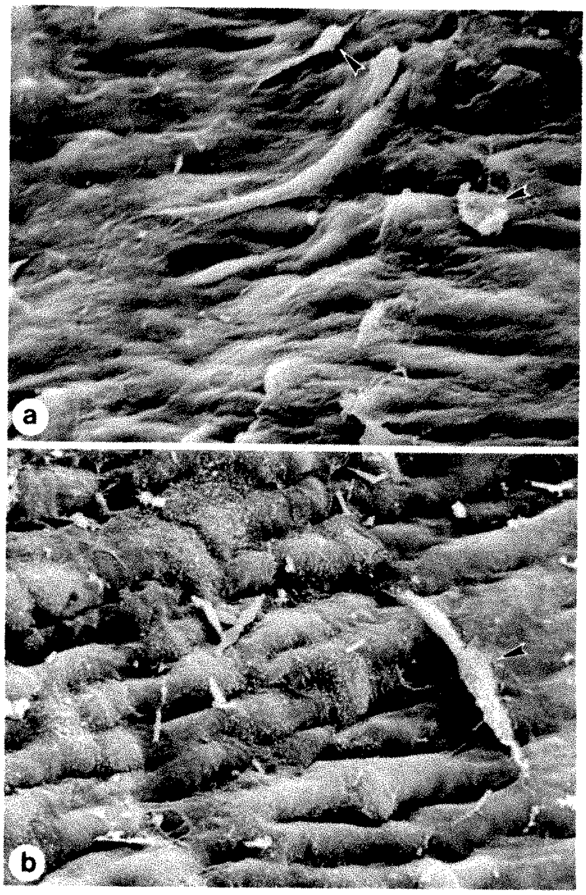

Fig 5. (A) Endothelial surface of veins immersed in blood (Group 4) shows occasional areas of endothelial cell separation with rolled-up appearance of a few cells (arrowheads). *Note the generally intact endothelial cell layer and normal nuclei. (×1,000 before 40% reduction.) (B) Endothelial surface of vein immersed in cold blood (Group 5) shows a single rolled-up endothelial cell* (arrowhead) *with good preservation of the remainder of the surface layer. Note prominent nuclei and microvilli. (×940 before 40% reduction.)*

Comment

Coronary artery vein graft patency rates drop dramatically during the first year following implantation, with reported patency rates of 50 to 85% at one year [12, 14, 15, 19, 29]. Animal studies suggest that 60% of failures occur within the first week, usually from thrombosis [5]. Following the high rate of attrition during the first year, occlusions occur at rates of less than 2% per year [8, 24]. These markedly different rates of early and late graft failure suggest that they result from two separate processes—early thrombosis and late luminal stenosis or occlusion.

Examination of postmortem and surgical specimens of vein grafts demonstrates that 70% of occlusions within the first year are secondary to mural thrombus formation overlying areas of endothelial cell loss [28]. Jones [16], Ferrans [13], Barboriak [3], Reiche [22], and their associates observed adherent fibrin and thrombus over denuded endothelium in vein grafts, while Bulkley and Hutchins [7] demonstrated circumferential intimal thrombus in 73% of human vein grafts obtained one hour to one month postoperatively. Studies of vein grafts in dogs have shown large areas of sloughed endothelium, leaving basement membrane, fibrillar collagen, and elastin to which microthrombi of platelets, red blood cells, and fibrin are adherent [5, 21, 27, 30]. Thus, denuding of intimal endothelium predisposes to mural thrombus formation, which, in turn, is a cause of early graft occlusion.

Late graft failures appear to arise from focal or diffuse luminal stenoses secondary to subendothelial fibromuscular hyperplasia or atheromatous plaques [2, 7, 13, 16, 28]. Medial necrosis, hydraulic alterations, arterialization of the vein wall, and venous valve stenosis have been implicated in the pathogenesis of fibromuscular hyperplasia [4–6, 14, 16, 17]. Although the fate of the original endothelium in implanted vein grafts is not known with certainty, after several months of implantation, the endothelium of vein grafts appears to be regenerated, presumably from endothelial cells remaining in the wall. Nevertheless, late endothelial deficits do occur [2, 3, 6, 28]. Additionally, intima underlying regenerated endothelium is substantially thicker and more likely to accumulate lipid than is intima under undamaged endothelium [20]. Studies by Duguid [10, 11], Jones and co-workers [16], and Ross and colleagues [23] have indicated that the development of late fibromuscular hyperplasia may be secondary to the formation and organization of early intimal thrombi and platelet-fibrin aggregates. A thrombotic origin of intimal hyperplasia is supported further by the finding that drugs that inhibit platelet aggregation and activation also reduce intimal thickening in animal coronary bypass grafts [19]. Thus, despite endothelial regeneration, the initial endothelial damage at operation may predispose to the late development of fibromuscular intimal hyperplasia, late graft stenosis, and late graft occlusion. Therefore, the preservation of the structural integrity of the vein appears to be important.

The results of our investigations indicate that the endothelium of human veins immersed in blood is better preserved than the endothelium of veins immersed in saline solution for identical time periods, at identical temperatures, and subjected to identical distention pressures. Immersion in cold blood provides additional protection for human veins, as suggested by animal experiments [1]. Furthermore, distention above physiological pressures with saline solution damages the vein intimal and medial components [1, 18, 25]. Vein wall edema is minimal or absent following blood immersion, whereas edema is consistently present following immersion in saline solution, especially when associated with high distention pressures.

In conclusion, human saphenous vein endothelium is damaged by intraoperative manipulation and particularly by immersion in saline solution and by distention to pressures above 100 mm Hg. Human saphenous veins are best preserved by gentle handling, immersion in cold, heparinized blood and avoidance of distention above physiological pressures. Preservation of the endothelium and prevention of mural edema may reduce early thrombus formation and the late development of subendothelial fibromuscular hyperplasia.

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Discussion

DR. GORDON N. OLINGER (Milwaukee, WI): I will accent Dr. Gundry's concern regarding trauma to veins by relating some biochemical data pertinent to the effect of trauma on delayed vein graft atherogenesis. I also will comment on the pressure limits for vein distention Dr. Gundry has advocated.

My data were derived from a nonhuman primate model developed at the laboratory at the Medical College of Wisconsin. A forearm cephalic vein was inserted as a reversed graft from the common femoral to the superficial femoral artery, bypassing an occlusive ligature. Before insertion, the distal half of the graft was distended with heparinized blood to 350 mm Hg and the proximal half to 700 mm Hg. The particular group of animals used was normolipemic, and grafts were harvested at three months. I believe this model is reasonably analogous to use of human saphenous vein as an artery replacement.

Monkeys' cephalic veins are muscular vessels like human saphenous veins, and the pressure required to overcome spasm in these veins is similar to that observed intraoperatively in human veins, that is, somewhere from 200 to as high as 500 mm Hg. This is more pressure than Dr. Gundry found suitable. I wonder if storage for one hour prior to distention—really a clinical impracticality in our practice—facilitated lower pressures in this study. My colleagues and I found by electron microscopy examination that endothelium of monkey veins distended at 300 mm Hg, seen prior to implantation, is generally well preserved. Higher pressure distention, on the other hand, denudes endothelium, exposing basement membrane and collagen to formed blood elements. Now 700 mm Hg may seem outrageously high, but such intraluminal pressures or greater ones are common when human saphenous veins are distended by the unfortunately popular technique of occluding one end and applying pressure to the other with a fluid-filled syringe.

When these grafts were harvested, biochemical analysis defined an increased concentration of cholesterol in grafts compared with normal vein left in situ, and a concentration of cholesterol in the higher pressure segments that was significantly greater than that in the lower pressure segments. The same relationships held for beta-apolipoprotein.

Thus, there are both histological and biochemical data to support the concept that intraoperative endothelial damage may be a precursor to vein graft atheromatous degeneration. Injury from hypooncotic agents can and should be avoided. However, if the surgeon wants to work with veins free from spasm, some intraluminal distending pressure will have to be applied. We found a range from 300 to 400 mm Hg to be necessary usually. Our observations suggest such pressures will permit preservation of endothelial integrity not only in monkey veins but, in contradistinction to Dr. Gundry's studies, in human saphenous veins as well.

At this time we are distending veins in the operating room with a simple pressure-limiting balloon device inserted between the syringe and vein that permits vein distention at less than 400 mm Hg. We hope it will help mitigate at least one of the factors in vein graft atherogenesis.

DR. GERALD M. LAWRIE (Houston, TX): I present some original data, compiled by Dr. Jack Titus and Dr. Saenz at Baylor, from 60 grafts recovered from the time of operation in humans to about two weeks after operation.

In a graft recovered 6 hours after operation, there is necrosis in the intima, some changes in the endothelium, and some edema. One day after operation, almost all the veins are lined by fibrin to which platelets are adhering and there are platelet thrombi. This may explain the dichotomy between the theoretical advantages of aspirin or Persantine (dipyridamole) and the practical effects. The process is well advanced long before any of these agents can be started.

Three days after operation, there is quite extensive necrosis developing progressively in the intima with pyknotic nuclei. Fibrin is overlying the endothelium, which has undergone patchy loss and has some edema. Nine days after operation, the fibrin lining is present, the entire vein wall is infiltrated with inflammatory cells, and the entire thickness of the vein wall has undergone patchy necrosis. This has occurred independent of the extent of intimal integrity.

Despite these early findings in long-term, follow-up pathological studies, findings that I think have not been documented before, we found excellent late histology. So although I think the early techniques used to prepare the veins are important, more work must be done to document what happens in the first two weeks. Our study leads us to believe that the veins universally undergo patchy, generalized necrosis regardless of the technique used to prepare them.

Late Survival Following Use of Intraaortic Balloon Pump in Revascularization Operations

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Delos M. Cosgrove, M.D., Paul C. Taylor, M.D., and Daniel F. Phillips, M.D.

ABSTRACT **The early and late results of intraaortic balloon pump (IABP) support in 197 patients with pure myocardial revascularization were analyzed. Group I, 61 patients, had IABP support initiated preoperatively; Group II, 99 patients, had IABP support in the operating room because of inability to be weaned from bypass; and Group III, 37 patients, had support instituted for persistent low cardiac output state in the postoperative period. The early results showed that 73% were discharged from the hospital and that delayed use of the IABP was associated with a high mortality and a high rate of perioperative myocardial infarction. When the results between men and women were compared, no statistical difference was noted. After a mean follow-up of 18 months, there were 9 late deaths. Three were due to noncardiac causes. The two-year cardiac actuarial survival for the hospital survivors was 96% and all three groups had uniformly good symptomatic relief. After hospital discharge, the late results of patients who required use of the IABP in conjunction with pure myocardial revascularization were the same as for patients who did not require IABP support.**

The use of the intraaortic balloon pump (IABP) in conjunction with cardiac operations results in improved hospital survival. This report analyzes the effect of timing of IABP use on the results of operation for pure revascularization and the survival of these patients following hospital discharge.

Material and Methods

From May, 1975, through December, 1978, 197 patients who had undergone myocardial revascularization were supported postoperatively for periods of 1 to 11 days (mean, 3.2 days). They represent 2.2% of 8,879 patients requiring revascularization in that period. Patients who had undergone valve operation alone or in combination with revascularization are not included in this series. These 197 patients were subdivided into three groups based on the timing of IABP insertion in relation to the surgical procedure [4].

Group I (61 patients, 31%) had the balloon inserted preoperatively. The indications were unstable angina in 35 patients, postinfarction angina in 11, poor preoperative ventricular function in 12, or cardiac arrest at the time of induction of anesthesia in 3, with multiple indications in 15 patients. The presence of severe obstruction of the left main trunk was not considered an indication.

Group II (99 patients, 50%) had IABP support instituted in the operating room when the patient could not be weaned from cardiopulmonary bypass. A subgroup of 22 patients who could not be weaned from cardiopulmonary bypass despite the IABP and maximal drug therapy is not included in this report.

Group III (37 patients, 19%) had IABP support instituted for low cardiac output state or uncontrollable arrhythmias or both despite attempted medical stabilization in the intensive care unit postoperatively.

A Datascope System 80 console actuated a 30 or 35 cc balloon in all patients. In our early experience, when a catheter could not be passed through either femoral artery because of severe peripheral atherosclerotic disease, IABP support was not used. More recently, in 5 patients the balloon catheter was inserted through the ascending aorta [12], and 3 survived.

The patients ranged from 28 to 79 years old (mean, 57.1 years) with a sex distribution of 167 men and 30 women, a ratio similar to that of patients having operation for uncomplicated

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Table 1. Extent of Coronary Artery Disease[a]

Group	SVD	DVD	TVD	LMT	Normal Ventricular Function Preop
I (61)	5	19	37	11	27
II (99)	7	23	69	29	51
III (37)	5	5	27	7	20

[a]Numbers are the numbers of patients involved.

SVD = single-vessel disease; DVD = double-vessel disease; TVD = triple-vessel disease; LMT = left main trunk.

myocardial revascularization. Most patients in all three groups had triple-vessel disease, and 50% had normal preoperative ventricular function (Table 1). An average of 2.5 grafts per patient was constructed, and complete revascularization (i.e., major coronary vessels that were narrowed more than 50% in lumen diameter received a bypass graft) was attained in 66.4% of patients.

Results

In Group I, the period of preoperative support with IABP ranged from 2 hours to 5 days. The mean duration of postoperative support was 3.2 days. The hospital mortality was 18% (11 patients) and 6 of them died while still being supported with the IABP (Table 2). Six patients had perioperative myocardial infarctions (new Q waves); 5 of these 6 died during balloon support and the sixth after the balloon was removed. Fifty patients were discharged from the hospital (82%), and there were 48 late survivors (78.6%) at a mean follow-up of 18 months. One late death was caused by myocardial infarction, and the second by carcinoma. Forty-four of the survivors (91.6%) had no recurrence of angina.

Table 2. Results of IABP and Coronary Artery Operation

Complication	Group I (%)	Group II (%)	Group III (%)
In-hospital mortality	18.0	27.2	43.2
Perioperative myocardial infarction	9.8	27.2	45.9
Late mortality	3.2	6.0	2.7

IABP = intraaortic balloon pump.

For Group II the mean duration of postoperative IABP support was 3.0 days. The hospital mortality was 27% (27 patients), and 27 perioperative myocardial infarctions were documented (see Table 2). Nine patients died of the infarction. Fourteen of the 27 patients who died could not be weaned from the balloon pump, and 8 of these 14 had perioperative myocardial infarction. Seventy-two patients (72.7%) were discharged from the hospital, and there were 6 late deaths after a mean follow-up of 18 months. Two patients had documented myocardial infarctions, 1 fatal, and 54 patients (75.0%) remain asymptomatic.

In Group III, the mean duration of IABP support was 3.6 days. Sixteen patients died postoperatively in the hospital (43.2%), and 17 had a documented perioperative infarction (45.9%) (see Table 2). Seven of the patients died while being supported on the balloon, and 6 of them had a perioperative myocardial infarction. Twenty-one patients (56%) were discharged from the hospital. There was 1 late cardiac death, and 18 patients (85.7%) were symptom-free.

There were complications associated with insertion of the balloon catheter. Failure to insert the balloon occurred in 15 patients (6.8%). Seventeen patients (8.6%) had evidence of leg ischemia. One required endarterectomy and patch graft following removal of the balloon catheter, and another had a small embolus to the great toe; it resolved spontaneously. All other patients had reversal of the ischemia after the balloon catheter was removed. In 1 patient (0.5%) with direct insertion in the ascending aorta, findings at postmortem examination disclosed an aortic dissection associated with this technique. Local groin wound infection was noted in 12 patients (6.1%), and 1 required removal of the residual graft to allow healing of the wound. In no patient did the local complications of the balloon catheter contribute to death. Late follow-up indicates that 3 survivors (2.2%) have varying degrees of foot drop and that 2 others (1.5%) have persistent numbness in the distribution of the femoral nerve.

Of the entire series of 197 patients supported

Table 3. Results with the IABP in 167 Men and 30 Women

Complication	Men	Women
Early mortality (%)	26.4	33.3
Early myocardial infarction (%)	25	26.7
Late mortality (%)	5.4[a]	0
Late myocardial infarction (%)	1.8	0

[a]includes 3 noncardiac deaths.

IABP = intraaortic balloon pump.

by the IABP, 143 patients (72.6%) were discharged from the hospital. Complete follow-up was obtained by written questionnaire or direct contact after a mean interval of 18 months (range, 6 to 40 months). The early and late results of balloon pumping did not differ between men and women (Table 3). There were 9 late deaths, 3 of noncardiac causes (carcinoma of the kidney, lung, and colon), for a late survival of 134 patients (68%). At late follow-up there have been 3 documented late myocardial infarctions with 2 deaths. Eighty-five percent of the surviving patients were asymptomatic, and 55% were fully employed at the time of this review.

Postoperative angiography was performed in 15 patients at a mean interval of 12.3 months because of recurrent angina in 7 or as a routine check in 8. Thirty-two of 36 grafts were found patent (88.8%), with an occluded graft in 3 of the 7 patients with recurrent angina. Five patients showed improved ventricular function, 5 were unchanged, and 5 demonstrated a new area or areas of ventricular impairment; 4 of the last were in Group II and 1 in Group III.

Comment

Following the first clinical success by Kantrowitz and associates [9] in 1968, the IABP was used mainly to support patients in cardiogenic shock secondary to myocardial infarction. Buckley and co-workers [5] recognized that the survival rate improved if the IABP was used in conjunction with corrective cardiac operations, especially in patients with unstable angina. Currently, its function to aid weaning from cardiopulmonary bypass or to support patients with low cardiac output in the immediate postoperative period is well established [1, 3, 8, 10, 13]. The use of the IABP preoperatively is controversial since stabilization preoperatively by aggressive medical therapy is now practiced widely [6, 7, 11].

The hospital survival of 72.6% in this series is higher than that found by some other groups [3, 7, 8, 10, 13], but this report is limited to patients undergoing revascularization operation and does not include the IABP used with valve operation or the combination of valve operation plus revascularization. We believe that better medical and anesthetic management of these patients in conjunction with improved intraoperative myocardial protection has had an important influence on these results. Our present indications for preoperative IABP use are unstable angina unresponsive to maximal medical therapy, postinfarction angina, or severely impaired ventricular function often in association with reoperation.

The early results in this series, even if the somewhat controversial Group I is excluded, show the better survival associated with earlier use of the IABP, a fact previously documented by Bolooki [1]. There was an obvious correlation between mortality and the incidence of perioperative infarction in Groups II and III. There was a low complication rate associated with use of the catheter and, more recently, we have had a limited experience with the percutaneously introduced balloon catheter [2, 14], which may decrease some of the morbidity associated with this procedure. Because of its ease and convenience, the use of the IABP preoperatively to stabilize patients may also be increased.

When the late results were considered, 3 of the 9 deaths were from noncardiac causes (carcinomas) and the two-year cardiac actuarial survival after discharge was 96%; 85% were asymptomatic. Further analysis of the 6 late cardiac deaths showed that 2 patients died during myocardial infarction, 2 died of congestive heart failure, and 2 died suddenly, presumably of arrhythmias or myocardial infarction. Five patients had diffuse, severe impairment of ventricular function preoperatively with end-diastolic pressures over 24 mm Hg, and 4 of the 6 had incomplete revascularization because of diffuse small-vessel atherosclerosis. These factors are known to affect adversely the long-term prognosis following revascularization operation. This series shows that while there are differences among the three groups in the early results, the long-term results for all patients surviving the hospital course were similar to those of patients undergoing revascularization operation and not requiring a balloon pump as part of the hospital course.

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Discussion

DR. ROBERT L. BERGER (Boston, MA): I enjoyed this paper and want to bring to your attention another mechanical pump or left ventricular assist device developed by Norman and Bernhard. This is a paracorporeal pneumatic pump that has a capacity of 8 liters per minute and that can be substituted for the entire left ventricular volume pressure work load. The device has been used at Boston University Medical Center in 12 patients in cardiogenic shock after cardiotomy, when massive catecholamine therapy and intraaortic balloon pumping failed.

The initial experience was educational but the results were dismal. However, among the last 5 patients are 2 long-term and 2 short-term survivors. The first success was almost two years ago, and the patient is still alive. The device supports the circulation satisfactorily without serious side-effects, and it unloads the left ventricle completely to permit recovery of the injured myocardium.

As we saw from the Cleveland Clinic experience, the intraaortic balloon is a useful support system but it is not powerful enough to cope with massive left ventricular damage. Based on our clinical experience, I believe that the left ventricular assist device is a most promising mechanical pump in instances of overwhelming but reversible failure of the left ventricle. At Boston University Medical Center, we are continuing our trials and plan to extend the use of the left ventricular assist device to patients in cardiogenic shock after infarction.

I wonder about the patient who had a dissection with the intraaortic balloon. Was the balloon in the true lumen or in the false lumen at postmortem examination?

DR. GOLDING: Thank you, Dr. Berger. I think the results that you are obtaining with the left ventricular assist device are very impressive. We also utilize a left ventricular assist device and have had 1 survivor out of 7 patients.

As for the patient who had a dissection, he was one of the patients who died. The balloon catheter was in the false lumen, and, as has been reported by others, it augmented normally. The final trace appeared to be a normal augmentation.

A Comparison of the Effects of Membrane and Bubble Oxygenators on Platelet Counts and Platelet Size in Elective Cardiac Operations

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ABSTRACT **To compare the effects of membrane and bubble oxygenators on platelet counts and the size of circulating platelets, serial hematocrits, platelet counts, and platelet sizing were measured in 23 patients undergoing elective cardiac operations. In 10 patients a bubble oxygenator was used and in 13, a SciMed membrane oxygenator. The two groups were statistically similar with respect to age, weight, time on bypass, and mean blood flow rates during bypass.**

It was found that platelet counts, when corrected for hemodilution, did not fall from control levels during or up to 24 hours after cardiopulmonary bypass in either group. In both groups, the relative number of platelets per gram of hemoglobin increased slightly during and after bypass, and this increase was significant in the bubble oxygenator group. The average size of circulating platelets increased only in the bubble oxygenator group, and then only in the one-day postoperative sample. These findings suggest that the membrane oxygenator offers no advantage with respect to preservation of platelets during cardiopulmonary bypass lasting up to 2 to 3 hours.

It is well known that platelet counts fall during cardiopulmonary bypass. It has been suggested that the mechanisms for this decrease could be platelet destruction [1], platelet aggregation and trapping within the extracorporeal circuit [15], or platelet sequestration within the liver, the lung, or other organs [2]. Several authors reported that platelet counts fall less precipitously when a membrane oxygenator is used instead of a bubble oxygenator [2, 11, 17, 18], and one argument put forth in favor of the routine use of membrane oxygenators in cardiac operations is that platelets will be spared [9, 11].

Based on observations in 12 patients, Laufer and co-workers [8] reported that large platelets (which are younger and more adhesive) are selectively removed from the circulation during the early minutes of cardiopulmonary bypass. Within 2 hours after termination of bypass, they found that large platelets are selectively released into the circulation. The present study was done to compare the effects of membrane and bubble oxygenators on platelet counts and the size of circulating platelets in patients having elective cardiac operations.

Material and Methods

Platelet counts and hematocrits were measured serially in 23 patients having elective cardiac operations using cardiopulmonary bypass. Measurements were done prior to bypass; at 5 minutes, 60 minutes, and 120 minutes of bypass; within 10 minutes of coming off bypass; on arrival in the recovery room; after 90 minutes in the recovery room; and on the morning of the first postoperative day. If blood was used in the priming solution (as it was in two of the bubble oxygenator perfusions and all of the membrane perfusions), platelet counts and hematocrits were also measured on the prime. Platelet sizing was done on a blood sample collected prior to bypass, after 90 minutes in the recovery room, and on the morning of the first postoperative day.

Patients scheduled for elective cardiac operation were assigned to either the membrane or bubble oxygenator group in a random manner after the responsible surgeon had indicated a willingness to have the patient participate in the study. Ten patients (7 men and 3 women) were in the bubble oxygenator group and 13 (8

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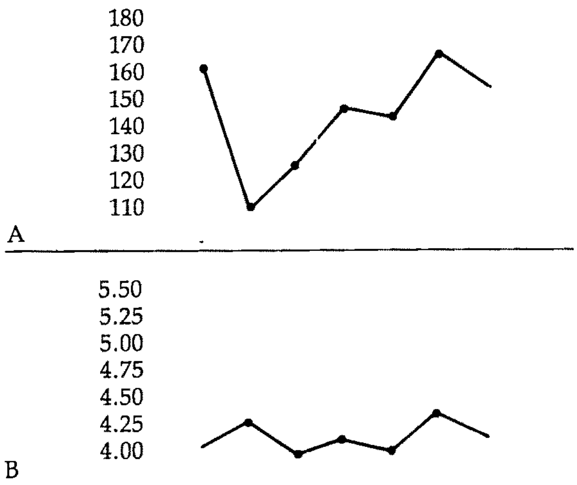

Fig 1. (A) Absolute platelet counts (× 10³) measured in Patient 15 without correction for hemodilution. (B) The same data expressed as platelet index after correction for hemodilution.

men and 5 women) in the membrane oxygenator group.

Platelet counts were done by the method of Rees and Ecker [13]. Platelet sizing was done using a calibrated microscope ocular micrometer with a magnification of 1,000, as described by Garg and colleagues [6]. Three hundred consecutive platelets were counted, and the number and percentage of platelets measuring 1.0 μ to 6.5 μ at each 0.5 μ increment were recorded. Mean platelet size for each sample was calculated. Individuals doing the platelet counts and platelet sizing did not know to which group the samples belonged.

Platelet counts were corrected for hemodilution by dividing each platelet count by the simultaneously measured hematocrit, thus yielding a "platelet index." This then could be directly compared with other platelet indices calculated from platelet counts measured at other levels of hemodilution. Figure 1 illustrates the usefulness of the platelet index. Part A shows absolute platelet counts measured in 1 of our patients plotted without correction for hemodilution. When compared with B, which shows the same data expressed as "platelet index" after correction for hemodilution, it can be seen that the apparent loss of platelets can be explained completely by dilution during cardiopulmonary bypass in this patient.

Platelet indices and sizes measured in each oxygenator group at different times in the experimental protocol were compared with control values for that group using the one-sample t test on differences. The same data were examined using the two-sample t statistic to compare the bubble oxygenator group with the membrane oxygenator group.

All membrane oxygenators were SciMed Kolobow spiral wound membranes, seven were 3.5 m^2 in size and six were 2.5 m^2. The membrane material was gum in twelve and silicone rubber in one. The winding tension in all of the gum membranes was 2.72 kg and in the silicon rubber unit, 3.18 kg. All membrane units were run with 50 mm Hg vacuum on the gas phase. A variety of bubble oxygenators was used. Four Bentley Q 100 units and three Bentley Q 200 A units were used. Two Harvey H 1000 oxygenators were used; and one Galen Optiflow adult unit was used.

Details concerning operative procedures, patients, and pump times and flows are shown in Table 1. The groups did not differ significantly in any variable listed. All patients had intravenous administration of Solu-Medrol (methyl

Table 1. Patient Data[a]

Data	Bubble Oxygenator (N = 10)	Membrane Oxygenator (N = 13)
Age (yr)	42–68 (55.5)	48–71 (59.7)
Weight (kg)	58.4–102 (78.7)	47–92 (69.1)
Type of operation	8 CAB; 1 MVR + CAB; 1 AVR	13 CAB
Bypass time (min)	52–180 (108.6)	44–129 (96.5)
Flow (ml/kg/min)	51.5–68.7 (60.0)	49.5–77.8 (65.9)

[a] All data except type of operation are given as the range with the mean in parentheses.

CAB = coronary artery bypass; MVR = mitral valve replacement; AVR = aortic valve replacement.

prednisolone sodium succinate), 30 mg per kilogram of body weight, prior to the institution of cardiopulmonary bypass, except 2 (both in the bubble oxygenator group). They might have received either 35 mg of dexamethasone or a placebo instead of methylprednisolone as part of another study.

Results

The groups did not differ significantly with respect to age, body weight, duration of perfusion, or perfusion flow rates (see Table 1). All patients in the membrane oxygenator group underwent only coronary artery bypass operation. Eight patients in the bubble oxygenator group had coronary bypass only, 1 had mitral valve replacement and single vessel coronary bypass, and 1 had aortic valve replacement.

Platelet index and sizing data are listed in Tables 2 and 3, and the same data are displayed graphically in Figures 2 and 3. In the membrane oxygenator group, platelet indices did not differ significantly from control values at any time in the experimental protocol ($p > 0.05$). Likewise, platelet sizes did not differ significantly from those obtained before bypass at any point of observation ($p > 0.05$).

In the bubble oxygenator group, all platelet indices measured subsequent to measurement of control values were larger than the control platelet index. This increase was significant at every point ($p < 0.05$) except two: the values obtained 5 minutes after coming off bypass and the values obtained on the first postoperative day ($p > 0.05$). However, if platelet indices at each subsequent time period are compared with values measured 5 minutes after going on the pump, no significant differences can be shown either during the remainder of the perfusion or subsequent to perfusion ($p > 0.05$). Platelet sizes measured 90 minutes after arrival in the recovery room did not differ significantly from sizes before bypass ($p > 0.1$), but mean platelet size on the first postoperative day was significantly greater ($p < 0.05$).

When indices are compared between bubble and membrane oxygenator groups for each time period, no significant differences can be shown ($p > 0.05$), with the sole exception of the sample collected just after coming off bypass. Then, platelet indices were significantly greater in the bubble oxygenator group ($p < 0.01$) (see Figure 2).

In comparing mean platelet sizes, there was no significant difference between groups either on the sample obtained before bypass or on that

Table 2. Platelet Index and Sizing Data for the Membrane Oxygenator Group

	Platelet Index									Sizing (μ)		
Patient No.	Control	Prime	5 Min	60 Min	120 Min	Off	Arrive Recovery Room	90 Min Recovery Room	1 D	Before Bypass	90 Min Recovery Room	1 D
1	3.37	4.95	3.96	3.79	...	...	4.05	5.11	...	...	...	...
2	4.36	2.94	4.64	4.36	...	...	4.54	4.58	...	...	...	...
3	4.32	4.22	3.11	4.74	...	...	4.00	5.32	...	...	...	...
4	4.89	4.82	5.97	5.77	...	...	5.03	5.11	...	...	...	...
7	5.35	6.06	5.48	4.46	...	4.46	3.68	3.87	4.49	2.48	2.38	2.05
12	3.74	2.85	4.65	4.36	...	3.30	5.06	4.17	4.39	2.45	2.48	2.38
13	4.62	4.83	5.08	5.11	...	4.39	4.56	4.79	4.72	2.50	2.54	2.56
14	5.03	4.56	4.75	5.13	5.00	5.00	4.83	4.35	4.13	2.52	2.48	2.54
15	4.13	5.50	4.29	4.10	...	4.20	4.06	4.45	4.19	2.42	2.43	2.51
16	3.86	3.64	4.40	...	...	3.93	5.40	3.95	4.66	2.35	2.46	2.36
17	4.00	4.60	4.73	4.19	...	4.03	3.39	3.40	4.13	2.33	2.48	2.35
18	3.95	4.26	3.48	4.26	3.93	3.93	3.31	3.31	4.03	2.32	2.27	2.31
19	4.60	5.25	4.91	4.30	...	4.70	4.62	4.32	4.84	2.27	2.20	2.36
Σ	56.22	58.48	59.45	54.57	8.93	37.94	56.53	56.73	39.58	21.64	21.72	21.42
$\overline{m}$	4.32	4.50	4.57	4.55	4.47	4.22	4.35	4.36	4.40	2.40	2.41	2.38
SD	0.56	0.93	0.77	0.55	0.76	0.50	0.66	0.63	0.30	0.09	0.11	0.15
SEM	0.16	0.26	0.21	0.16	0.53	0.17	0.18	0.17	0.10	0.03	0.04	0.05

Σ = sum; $\overline{m}$ = mean; SD = standard deviation; SEM = standard error of the mean.

Table 3. Platelet Index and Sizing Data for the Bubble Oxygenator Group

	Platelet Index									Sizing (μ)		
Patient No.	Control	Prime	5 Min	60 Min	120 Min	Off	Arrive Recovery Room	90 Min Recovery Room	1 D	Before Bypass	90 Min Recovery Room	1 D
5	4.55	...	4.97	4.08	...	4.27	...	4.12	5.45	2.21	2.08	2.17
6	4.19	4.84	4.15	4.93	...	4.37	...	5.40	5.00	2.35	2.29	2.46
8	3.46	5.44	4.11	4.85	4.88	4.58	5.11	5.14	...	2.48	2.34	...
9	4.55	...	5.10	4.72	...	4.37	4.36	4.62	3.25	2.35	2.42	2.51
10	4.08	...	5.12	5.13	4.93	5.11	4.29	4.85	5.03	2.38	2.35	2.71
11	4.73	...	4.32	4.67	...	5.10	5.33	5.31	4.72	2.45	2.49	2.45
20	3.60	...	4.34	4.00	4.24	4.24	3.51	4.10	3.61	2.39	2.38	2.45
21	3.62	...	4.09	4.05	4.08	4.42	4.03	3.71	4.00	2.35	2.37	2.46
22	4.07	...	4.27	4.49	...	4.49	4.51	4.41	4.72	...	2.30	2.31
23	3.85	...	4.39	4.38	...	5.92	...	4.53	4.85	1.57	1.95	...
Σ	40.70	10.28	44.86	45.30	18.13	46.87	31.14	46.19	40.63	20.53	22.97	19.52
$\bar{m}$	4.07	5.14	4.49	4.53	4.53	4.69	4.45	4.62	4.51	2.28	2.30	2.44
SD	0.44	0.42	0.41	0.40	0.44	0.53	0.62	0.56	0.73	0.28	0.16	0.16
SEM	0.14	0.30	0.13	0.13	0.22	0.17	0.23	0.18	0.24	0.09	0.05	0.05

Abbreviations same as for Table 2.

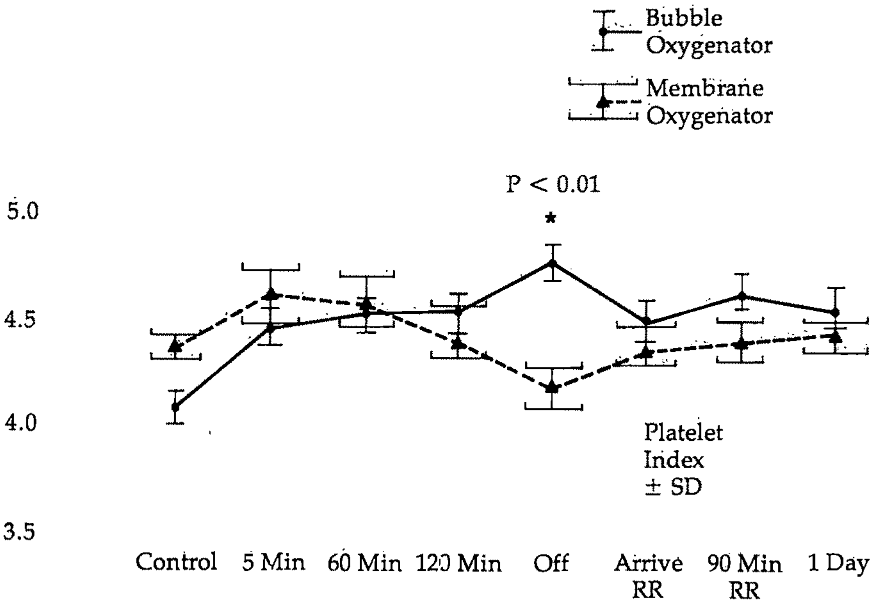

Fig 2. Platelet index data for bubble and membrane oxygenator groups. (SD = *standard deviation;* RR = *recovery room.)*

of the first day ($p > 0.05$). Mean platelet size was significantly larger in the membrane oxygenator group only on the sample collected 90 minutes after arrival in the recovery room ($p < 0.05$) (see Fig 3).

Comment

After twenty-five years of experience with clinical cardiopulmonary bypass, we still do not know precisely what happens to platelets during extracorporeal circulation. It is most commonly reported that platelet counts fall rapidly after the institution of bypass, slowly increase during bypass, and return to or exceed control levels some days after bypass [10, 12, 14, 16]. Since none of these studies accounted for the effect of hemodilution, it is not clear whether there was a greater loss of platelets than of hemoglobin. Salzman [14], however, stated that falls in platelet counts that he observed were too great to be accounted for by dilution alone. Only the report of Kolobow and colleagues [7]

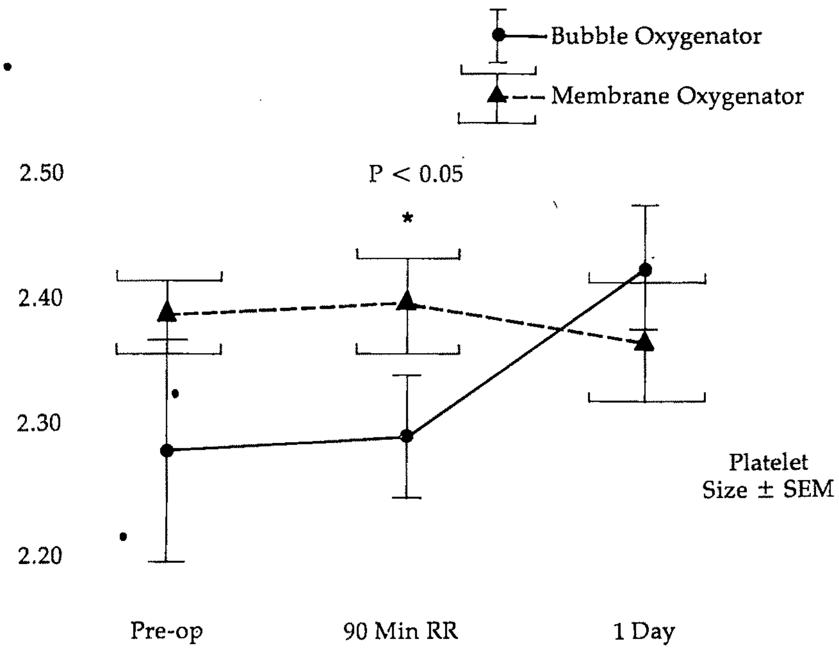

Fig 3. Platelet size (μ) data for bubble and membrane oxygenator groups. (SEM = *standard error of the mean;* RR = *recovery room.)*

showed platelet counts remaining in the normal or elevated range during long-term venovenous bypass with and without a membrane oxygenator in the circuit. Our study supports the concept that platelets are diluted but not lost during cardiopulmonary bypass of up to 3 hours. In fact, our data show that when one corrects for the effect of hemodilution, the number of platelets per gram of hemoglobin actually increases slightly during and after perfusion with the use of both bubble and membrane oxygenators (see Fig 2).

A number of investigators have reported that fewer platelets are lost with a membrane oxygenator in the circuit than with a bubble oxygenator [2, 11, 17, 18]. This study does not support that finding, but confirms the findings of Dutton [3], Wright [19], and their associates that platelet counts are equally well preserved whether a membrane or bubble oxygenator is used.

It may be of importance that all of our patients except 2 underwent operation for myocardial revascularization only. Except in the 2 who had valve replacement (both in the bubble oxygenator group), our use of cardiotomy suction was nil. This may have influenced our results. Edmunds and co-workers [4] measured cardiotomy suction return in a group of 76 pediatric patients and clearly demonstrated that the loss of platelets during perfusion was directly related to the percentage of total perfusate returned by cardiotomy suction.

Laufer and associates [8] studied the influence of bypass on platelet size using an electronic sizing apparatus based on the Coulter counter and reported that early in bypass, large platelets (which are younger and more adhesive) disappear first from the circulation and are selectively released into the circulation at the conclusion of bypass. Using a microscope ocular micrometer technique of directly measuring platelets, we could not confirm those findings, although we did not include sizing of platelets sampled during bypass as a part of our protocol. However, on samples taken 90 minutes after the conclusion of operation, we could not confirm an increase in the average platelet size or an increased percentage of large platelets in either group. Only in the bubble oxygenator group did we note an increase in mean platelet size and then only in the sample made one day postoperatively. The reason for the difference in these findings is not clear. One possible explanation is that an electronic counter such as that used by Laufer and co-workers [8] could have counted red cell fragments and other debris produced during bypass as "large platelets," an error avoided in the direct counting method. The question deserves further study.

We wish to emphasize that in this study we did not measure any factor of platelet function. It is known that platelet dysfunction is a regular consequence of cardiopulmonary bypass. Friedenberg and associates [5] evaluated platelet function in 40 patients before and after cardiopulmonary bypass using both bubble and membrane oxygenators, and showed that platelet aggregation induced by epinephrine, collagen, and adenosine diphosphate was regularly depressed. They found a decrease in the uptake and release of serotonin labeled with carbon 14 after bypass, and by electron microscopy of platelets after bypass, they showed a decrease in the number of dense granules, increased numbers of vacuoles, and marked membrane derangements—implying that platelets lose their storage pool during cardiopulmonary bypass. They believed that there was no difference in the degree of induced platelet dysfunction relative to the type of oxygenator used. If that is true, then that fact combined with the findings of this study suggest no advantage of either membrane or bubble oxygenator with respect to the preservation of platelets or the degree of induced platelet dysfunction in perfusions of up to 3 hours' duration.

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Platelet Loss during Experimental Cardiopulmonary Bypass and Its Prevention with Prostacyclin

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ABSTRACT **Prostacyclin (PGI_2), a newly discovered short-acting prostaglandin that inhibits platelet aggregation, was evaluated as an agent for prevention of cardiopulmonary bypass–induced thrombocytopenia. Ten adult, splenectomized greyhounds were divided into three treatment groups prior to beginning 120 minutes of partial cardiopulmonary bypass. Group 1 animals received 300 units of heparin per kilogram of body weight, Group 2 animals received 300 units of heparin per kilogram plus PGI_2, 1.5 μg per minute, and Group 3 animals received 300 units of heparin per kilogram plus PGI_2 3.0 μg per minute. Bypass and PGI_2 infusion were started simultaneously.**

Mean platelet counts of each group at 5 minutes were approximately 40% of prebypass levels. Additional platelet loss was seen in Groups 1 and 2 at 30, 60, and 120 minutes. However in Group 3, platelet counts at 30 and 60 minutes were essentially unchanged from prebypass levels. At 30, 60, and 120 minutes of cardiopulmonary bypass, the differences between Groups 1 and 3, and 2 and 3 are highly significant ($p < 0.01$).

We conclude that PGI_2 is an effective agent for preserving platelet levels during experimental cardiopulmonary bypass. Furthermore, it is possible that platelet loss during cardiopulmonary bypass may be caused, in part, by an imbalance between PGI_2 and thromboxane A_2, which results in excessive platelet adhesion and aggregation.

Thrombocytopenia is a common problem after cardiopulmonary bypass operation [5, 15, 21, 22] and predisposes patients to potentially serious hemorrhagic events. In an effort to prevent this occurrence, investigators have turned to pharmacological platelet inhibitors like aspirin, dipyridamole, and prostaglandin E_1 (PGE_1) with varying degrees of success [2, 17]. While aspirin (65 mg per kilogram of body weight) has been shown to be ineffective in preventing platelet loss, dipyridamole (4 mg per kilogram) moderately reduces platelet losses in dogs [17]. PGE_1, a prostaglandin with antiaggregatory activity, has no consistently beneficial effects on platelet counts during cardiopulmonary bypass in monkeys [2], but can reduce platelet loss during ex vivo recirculation of human and monkey blood through a pump oxygenator apparatus [1]. Therefore, the need still exists for an agent able to prevent platelet loss during cardiopulmonary bypass. Finding such an agent also should aid in the elucidation of the mechanism whereby platelets are lost during the procedure.

Prostacyclin (PGI_2) is a potentially useful agent for platelet preservation during cardiopulmonary bypass. While it is the most potent antiaggregatory agent yet discovered, the antiplatelet action of PGI_2 is short-lived [19]. Thus, normal platelet function returns soon after administration of the agent is discontinued [14]. Woods and colleagues [24] demonstrated that PGI_2 alone, without the use of heparin, prevents platelet loss during hemodialysis in dogs. We report here our experience using PGI_2 during cardiopulmonary bypass in dogs and propose a theory on the relationship between this agent and platelet loss during this procedure.

Material and Methods

Ten adult greyhound dogs weighing 23 to 28 kg were anesthetized with pentobarbital, 30 mg per kilogram of body weight. The dogs were

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ventilated with a volume ventilator (Bird model Mark VII) through a cuffed endotracheal tube throughout the experiment.

A splenectomy was performed on all dogs immediately prior to cardiopulmonary bypass to prevent a flux of blood components between the spleen and the intravascular space [3]. The dogs were systemically heparinized with beef lung heparin, 300 units per kilogram, from the Upjohn Company. Cannulation of the external jugular vein and bilateral femoral veins provided venous return, and arterial perfusion was accomplished through a femoral artery.

All dogs were perfused at a blood flow rate of 70 ml per kilogram with a barely occlusive, calibrated double-roller Travenol pump (model 500) for 120 minutes. Oxygen, carbon dioxide, and heat exchange were provided by a Harvey oxygenator (model H-100). The oxygen to blood flow ratio was 2:1, and the perfusate temperature was maintained at 37°C. The oxygenator and tubing were primed with 1,500 ml of lactated Ringer's solution. A Bentley blood filter (model PF-427) was placed in the arterial line for emboli filtration.

Solutions of PGI_2 were freshly prepared using PGI_2 sodium salt* (1.14 mg = 1.0 mg free acid equivalents PGI_2) and BuffAR pH 10 (Mallinckrodt). The final concentration of the solution was 10 μg of PGI_2 per milliliter. The solution was infused with an IVAC constant infusion pump (model 200) into the venous port of the oxygenator.

Group 1 animals (n = 4) did not receive any PGI_2. Group 2 (n = 3) animals received 1.5 μg of PGI_2 per minute. Group 3 animals (n = 3) received 3.0 μg of PGI_2 per minute. Infusion of PGI_2 was begun at the time bypass was instituted.

Data were collected immediately before bypass and 5, 30, 60, and 120 minutes into bypass. Microhematocrits were determined with an Internation Micro-Capillary Centrifuge model MB. Platelet counts (phase contrast microscopy) were performed by the clinical laboratory without knowledge of the experimental procedure [4]. Radial artery pressures were monitored with a Trantec pressure transducer (model 800) connected to an Electronics for Medicine monitor (model VR-6). A two-tailed, unpaired Student's t test was applied to the data to determine statistical significance.

Results

Results at 5 Minutes

Platelet counts, expressed as percent of prebypass levels (mean ± standard deviation), initially fell in all three groups (Fig 1). Although platelet counts could be expected to fall with the clear fluid prime, the observed decline exceeded that expected from dilution alone (Fig

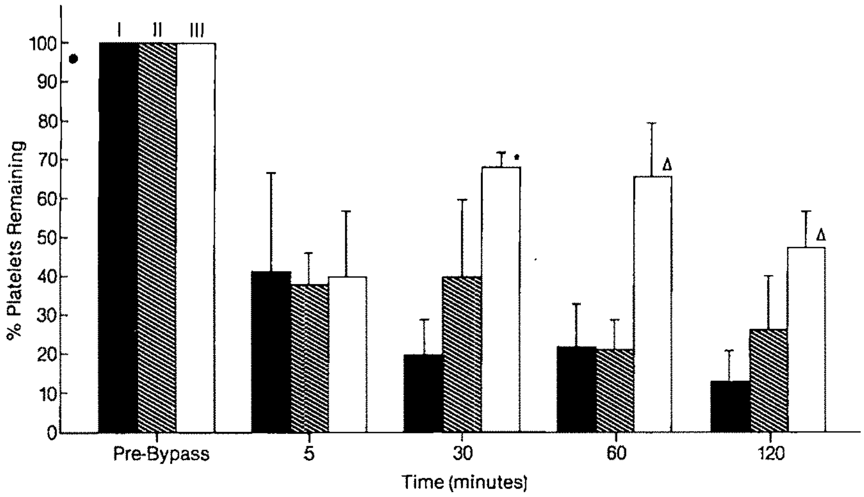

Fig 1. Platelet counts, expressed as percent of prebypass values, of Groups 1, 2, and 3 plotted versus time. Differences between Groups 1 and 3 and between Groups 2 and 3 are significant at 30, 60. and 120 minutes. Values are mean ± 1 standard deviation. (= p < 0.001; Δ = p < 0.01.)*

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*Kindly supplied by Dr. John Fike, The Upjohn Company, Kalamazoo, MI.

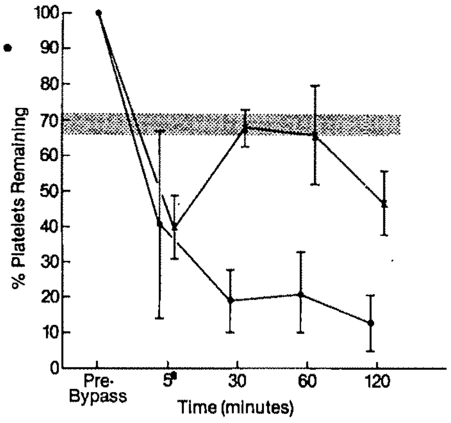


Fig 2. Platelet counts, expressed as percent of prebypass values, of Groups 1 (•) and 3 (X) *plotted versus time. Dotted area shows the expected effect of dilution alone on platelet counts. Differences between Groups 1 and 3 at 30 minutes and at 60 and 120 minutes are significant* ($p < 0.001$ *and* $p < 0.01$, *respectively). Values are mean ± 1 standard deviation.*

2). The dilution factor was calculated from the mean changes in hematocrits at 5 minutes from prebypass levels. There were no significant differences between groups with respect to 5-minute platelet counts.

Results at 30 Minutes

The platelet counts in Group 1 continued to fall to a mean value of 20 ± 9% of the prebypass level. No significant change occurred between 5 minutes and 30 minutes in Group 2. However, compared with control, mean platelet counts in Group 3 rose significantly during this interval to a mean value of 68 ± 4% of the prebypass level, within the range of platelet counts expected from dilution alone. These values in Group 3, unlike Group 2, were significantly higher than in Group 1 ($p < 0.001$).

Results at 60 Minutes

While the platelet counts of Groups 1 and 2 remained at approximately 20% of control, the mean value of Group 3, 66 ± 12% of control, remained within the range expected by dilution alone. The differences between Groups 1 and 3 and between Groups 2 and 3 were significant ($p < 0.01$).

Results at 120 Minutes

The mean platelet counts relative to control for Group 3, 47 ± 8%, remained higher than those in either Group 1, 13 ± 9%, or Group 2, 27 ± 12% ($p < 0.01$). However, it did fall below the previously mentioned dilution range.

Comment

At normal concentrations, PGI_2 inhibits platelet aggregation and at higher concentrations, platelet adhesion [14, 18, 19, 20]. Furthermore, even higher levels of PGI_2 can cause deaggregation of recently formed platelet clumps [10, 12]. These effects of PGI_2 seem to be mediated through the stimulation of adenylate cyclase, which, in turn, leads to increased levels of platelet cAMP [7–9, 23].

Prostacyclin biosynthesis occurs mainly in healthy pulmonary and vascular endothelial cells [4, 11, 23] where PGI_2 synthetase converts endogenous precursors or platelet-liberated endoperoxides to PGI_2 [19]. Since its blood half-life is only 2 to 3 minutes [6, 13], these tissues must produce PGI_2 continuously to maintain effective, circulating concentrations [4].

In contrast to PGI_2, prostaglandin endoperoxides and principally thromboxane A_2 (TXA_2) have an anti-cAMP activity in platelets (Fig 3) [7–9, 23]. These substances, which are produced by platelets and damaged blood vessels, promote platelet adhesion and aggregation by decreasing platelet cAMP [7–9, 19, 23]. Certainly, collagen, epinephrine, adenosine diphosphate, and other substances also contribute to platelet homeostasis, but recent evidence indicates that PGI_2 and TXA_2 play key roles in controlling platelet function in vivo [7–9, 23].

With respect to the involvement of PGI_2 and TXA_2 in platelet homeostasis, it is presently thought that under normal conditions, circulating levels of PGI_2 are sufficient to offset the pro-aggregating influence of TXA_2 and prevent spontaneous aggregation and adherence of platelets to endothelium. However, when the endothelium is damaged, platelets congregate at the site and undergo a shape change, releasing the contents of their storage granules. Concentrations of endoperoxides and TXA_2 increase as the thrombus grows, further promoting platelet aggregation and adhesion. In general, this process has only a local effect, due to the short biological half-life of TXA_2, the circulating levels of PGI_2, and the conversion of platelet-

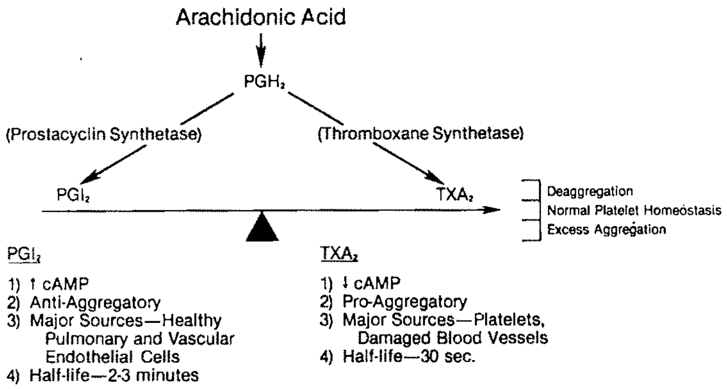


Fig 3. Although prostacyclin (PGI_2) *and thromboxane* A_2 (TXA_2) *are biosynthesized from common precursors, they are produced by different tissues and have opposing effects on platelets. It has been proposed that a balance system consisting of* TXA_2 *and* PGI_2*, as shown here, plays a major role in controlling platelet activity.*

liberated endoperoxides to PGI_2 by normal vascular endothelium surrounding the lesion. It is a system capable of quickly establishing hemostasis without undue obstruction of blood flow by limiting the size of the thrombus.

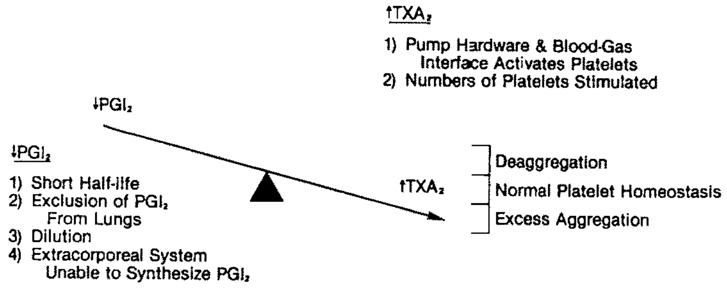
During extracorporeal circulation, these basic mechanisms are altered (Fig 4). Since PGI_2 is provided primarily by the lung [11, 13] and healthy vascular endothelium, blood is shunted around the major site of biosynthesis. The effect of any residual production of PGI_2 is diluted by the increased plasma volume required for the bypass procedure. Also, platelet contact with artificial surfaces [5, 15] and the presence of a blood-gas interface [17] have been proposed as factors precipitating platelet release of pro-aggregating endoperoxides and TXA_2.

We propose that there is an imbalance between PGI_2 and TXA_2 in the extracorporeal system and that it favors platelet adhesion and aggregation. This imbalance could be caused by decreasing levels of PGI_2, increased production of TXA_2, or, most likely, a combination of the two. The results of our experiment support this theory. Because we began infusions of PGI_2 into the venous port of the oxygenator precisely when bypass was instituted, we would expect to see little, if any, effect of the PGI_2 on 5-minute platelet counts. As shown in Figure 1, there were no significant differences among the three groups at that time.

While animals in the control group (Group 1) had a further decrease in platelet numbers at 30 minutes to 20% of prebypass levels, animals receiving 3 μg of PGI_2 per minute (Group 3) had platelet counts in the range expected by dilution alone. In other words, platelet counts of these animals were indistinguishable from prebypass values corrected for dilution. This difference is highly significant ($p < 0.001$) and deserves further explanation.

Prostacyclin, while being a potent inhibitor of platelet aggregation, also possesses the

Fig 4. Effects of cardiopulmonary bypass on the balance between prostacyclin (PGI_2) *and thromboxane* A_2 (TXA_2)*. Increased levels of* TXA_2 *and decreased levels of* PGI_2 *promote excess platelet adhesion and aggregation and result in thrombocytopenia. Administration of exogenous* PGI_2 *during cardiopulmonary bypass reestablishes the balance and prevents platelet loss.*


↑TXA₂
1) Pump Hardware & Blood-Gas Interface Activates Platelets
2) Numbers of Platelets Stimulated
↓PGI₂
↓PGI₂
1) Short Half-life
2) Exclusion of PGI₂ From Lungs
3) Dilution
4) Extracorporeal System Unable to Synthesize PGI₂
↑TXA₂
Deaggregation
Normal Platelet Homeostasis
Excess Aggregation

ability to disperse platelet clumps. Gryglewski and colleagues [10] demonstrated that PGI_2 disintegrates platelet aggregates, even after three hours. As the concentration of PGI_2 in our system increased, it is probable that platelet clumps formed during the period when the concentration of PGI_2 was inadequate deaggregated into individual platelets. Platelet counts would seem to rise, as shown in our data, but there is no real change in numbers of platelets, only in their location. Although PGI_2 was not yet identified at the time that Mielke and coworkers [17] did their study, their animals given the phosphodiesterase inhibitor, dipyridamole, showed a similar, albeit, less dramatic effect.

The lack of effect of PGI_2 on Group 2 animals was unexpected, but is explained readily. In our original design, we chose that dose of PGI_2 because it had been used successfully to prevent thrombocytopenia during hemodialysis [24]. However, this did not take into account the important dilution that occurs during cardiopulmonary bypass. Thus, the actual circulating concentration was only 60 to 70% of expected. Doubling the dose of PGI_2 produced dramatic platelet preservation, as evidenced by Group 3 values.

Longmore and associates [16] reported in 1979 that PGI_2, alone or in combination with heparin, prevented thrombocytopenia in nonsplenectomized greyhounds undergoing two hours of complete cardiopulmonary bypass. Platelet function returned to normal within 30 minutes of discontinuing the infusions. The dose of PGI_2 was five to ten times the dose used in our study.

Prostacyclin is effective in maintaining platelet counts during experimental cardiopulmonary bypass. The hypothesized relationship between alterations in the $PGI_2:TXA_2$ ratio and thrombocytopenia seen after this procedure has already been expressed. Since PGI_2 is still classified as an investigational drug, the results of future clinical trials will help to define its role in the prevention of platelet loss during human cardiopulmonary bypass.

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Notice from the Southern Thoracic Surgical Association

The Twenty-seventh Annual Meeting of the Southern Thoracic Surgical Association will be held at the Greenbriar, White Sulphur Springs, WV, Nov 13–15, 1980. There will be a $100 registration fee for nonmember physicians except for guest speakers, authors and co-authors on the program, and residents.

Applications for membership should be completed by Sept 1, 1980, and forwarded to E. P. Smith, Jr., M.D., 425 S Bath Club Blvd, N Redington Beach, FL 33708.

Richard B. McElvein, M.D.
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Experimental Endocarditis in Calf after Tricuspid Valve Replacement

Edwin L. Grogan, M.D., Merle A. Sande, M.D., Richard E. Clark, M.D.,
and Stanton P. Nolan, M.D.

ABSTRACT **A calf model for reproducible, prosthetic tricuspid valve endocarditis was developed using *Staphylococcus aureus.* The course of late prosthetic valve endocarditis was characterized as a fulminant disease when untreated with antibiotics. The earliest sign of a colonized valve prosthesis was an elevation of body temperature, which correlated with occurrence of positive blood cultures. The dose required to colonize an endothelialized tricuspid prosthetic valve in the calf model was 10^7 to 10^8 *S. aureus* organisms. In the model for late prosthetic valve endocarditis, silver-allantoin-heparin (SAH) treatment of the prosthetic valve gave no protection from inoculums of 10^8 *S. aureus* injected 60 days after operation. SAH treatment may be beneficial in early stages of prosthetic valve endocarditis, but this requires further study. Simultaneous cultures from the right atrium, the right ventricle, and the aorta of 2 animals showed that there was a 1,000- to 10,000-fold decrease in the bacterial titers across the combined pulmonary and systemic capillary beds. Bacterial titers drawn from the jugular vein had a 46% false negative result, and positive cultures from the external jugular vein showed only 1.3 *S. aureus* organisms per milliliter of blood. These bacteriological findings point out the risks of depending on sampling from the peripheral venous system when culturing for right heart endocarditis.**

Prosthetic valve endocarditis is an important, frequently lethal complication of cardiac valve replacement. It occurs in 1 to 4% of patients with artificial heart valves [6, 9, 13]. The incidence is highest in the first 60 days after operation. The organisms responsible for early endocarditis are frequently those isolated from the surgical field, i.e., *Staphylococcus epidermidis* and various corynebacteria [14]. In late prosthetic valve endocarditis ("late" defined as 60 or more days after valve replacement), the organisms isolated are those seen in endocarditis occurring on natural valves. Streptococci are common, although staphylococci, gram-negative bacilli, and fungi also produce disease [6, 15].

It has been shown in an animal model that development of nonprosthetic valve endocarditis correlates closely with the number of organisms injected [10]. Right-sided prosthetic valve endocarditis has been produced by giving a large inoculum of *Staphylococcus aureus* and has been prevented by antibiotic prophylaxis [5]. However, the clinical course of right-sided prosthetic valve endocarditis has not been well characterized experimentally, and the lowest infecting inoculum required to produce prosthetic valve endocarditis is not known.

Silver-allantoin has been shown to have antibacterial properties as a solution, a cream, or a surface treatment to sutures [1, 7, 12]. Silver-allantoin-heparin (SAH) treatment of vascular grafts has also been shown to be effective in preventing graft infections by *S. aureus* in a dog model [7]. SAH treatment of prosthetic heart valves has not been studied in early or late endocarditis animal models.

The purposes of this study were as follows: (1) to develop and characterize an animal model of late tricuspid prosthetic valve endocarditis; (2) to determine the inoculum size of *S. aureus* required to produce prosthetic valve endocarditis two months after implantation; and (3) to determine if SAH treatment of the cloth covering of the prosthetic valve afforded protection from the development of late endocarditis.

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Material and Methods

Operative Technique

The tricuspid valve was replaced in calves weighing 63 to 83 kg. Anesthesia was induced with halothane, and the animals were ventilated through an endotracheal tube. Venous and arterial pressures and arterial blood gases were measured. Meticulous sterile technique was used. Using cardiopulmonary bypass, the tricuspid valve was replaced through a right thoracotomy. The prosthesis used was a 30-M Braunwald-Cutter valve,* which was modified by covering the metal with fine mesh polyester fabric instead of the polytetrafluoroethylene used commercially, because the SAH complex would not bind to the latter material. The valve was secured to the annulus with interrupted 3-0 Tycron sutures. Once the calves had recovered from anesthesia, the endotracheal tube and intravascular catheters were removed.

Test Organisms

A double-blind method was used in which half of the implanted valve prostheses were pretreated with the SAH complex and the other half were untreated. The calves receiving the untreated prostheses were retrospectively labeled Group A, and those implanted with prostheses pretreated with SAH were labeled Group B. The organism used to produce bacterial endocarditis was a strain of *S. aureus* isolated from a patient with prosthetic valve endocarditis and previously characterized [11]. This strain is easily identified by a slow mannitol reaction, which obviates the bacteriophage typing. The inoculum was prepared in broth from an 18-hour culture and was then serially diluted in saline solution to the appropriate concentration. A split aliquot was cultured quantitatively to determine the exact inoculum that had been injected.

Experimental Design of Late Prosthetic Valve Endocarditis

Seven calves that survived the operative procedure were used in the study of late prosthetic valve endocarditis. Four animals had untreated valves and 3 had SAH-treated valves. These animals were given the first injection of *S. aureus* two months after tricuspid valve replacement. The injection was administered in the external jugular vein over a one-minute period. Prior to injection, rectal temperature was recorded and blood was taken for culture. After injection, rectal temperatures and blood were obtained daily. Blood for culture was obtained aseptically by withdrawing 10 ml from the external jugular vein. Pour plates were made in quantitative 10-fold dilutions of trypticase soy agar and counted at 48 hours. Daily observations of the heart sounds, jugular venous distention, and activity of the animals were made. If clinical or bacterial signs of prosthetic valve endocarditis did not develop in 10 to 14 days, the concentration of the inoculum was increased by a factor of 10 (one log) and the injection repeated until all animals had endocarditis.

All animals with prosthetic valve endocarditis died or were killed under general anesthesia in the moribund state. In 2 animals, after echocardiography and an aseptic thoracotomy, blood for culture was obtained simultaneously from the jugular vein, the right atrium, the right ventricle, and the aorta. In all animals the heart was removed using aseptic technique. Quantitative cultures of the homogenized vegetations were taken from the atrial and the ventricular sides of the prosthesis. Microscopic slides were prepared of the polyester fabric and overlying vegetations. Routine hematoxylin and eosin as well as Brown and Hopps bacterial stains were used. The vasculature of the lungs was inspected, and in some animals, histological sections were made.

Early Endocarditis

Immediately after completion of the tricuspid valve replacement, 4 calves had injection of 10^2 to 10^3 *S. aureus* organisms into the sewing collar of the prosthesis with the heart open. Two prostheses were treated with SAH. No antimicrobial agents were used in the postoperative period. Daily observations of heart sounds, jugular venous distention, and activity were made. Blood for culture was obtained periodically during the first 60 days after operation.

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*Generously supplied by Cutter Laboratories, San Diego, CA 92111.

Results

Infecting Dose for Late Prosthetic Valve Endocarditis

Four animals with untreated valves served as Group A. To determine the size of inoculum required to produce prosthetic valve endocarditis, 1 animal was inoculated serially with 10^4, 10^5, and 10^6 *S. aureus.* This animal was killed after the last injection. Cultures from the blood and valve were sterile. Two other animals initially were inoculated with 3.5×10^6 and 6.8×10^6 *S. aureus;* prosthetic valve endocarditis did not develop (Fig 1). However, an infection developed in both animals following injection with 6.9×10^7 and 3.9×10^8 *S. aureus.* An infection developed with the first inoculation in 1 animal injected with 3.9×10^7 *S. aureus.* Postoperatively, this calf failed to thrive and had lost 3 kg at two months. The other animals all gained from 22 to 30 kg at the 60-day interval.

No infection developed in the 3 animals with SAH-treated prostheses (Group B) following injection of 3.5×10^5, 3.9×10^6, and 6.8×10^7 *S. aureus.* Infection did occur following injections of 5.4×10^7, 6.9×10^7, and 3.9×10^8 *S. aureus.* There was no apparent difference between the infecting dose in animals with SAH-treated valves and in animals with untreated valves. Both groups had infection with greater than 10^7 organisms and did not have endocarditis with less than 10^7 organisms.

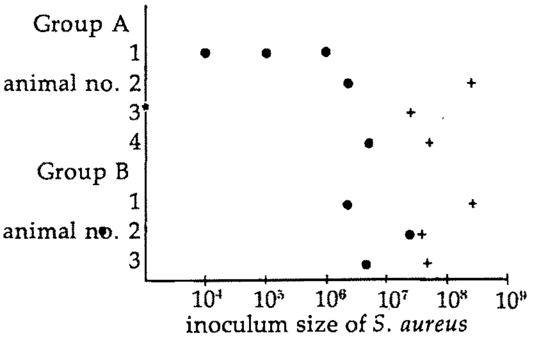

*Fig 1. Group A animals were implanted with untreated tricuspid prostheses. The infecting inoculum was between 3.9×10^7 and 3.9×10^8. Group B animals were implanted with tricuspid prostheses pretreated with the silver-allantoin-heparin complex. The infecting inoculum was between 5.4×10^7 and 3.9×10^8. (PVE = prosthetic valve endocarditis; ● = inoculum not producing PVE; + = inoculum producing PVE; * = failure to thrive after operation.)*

Clinical Course of Late Prosthetic Valve Endocarditis

The natural history of the disease process of late prosthetic valve endocarditis is depicted in Figure 2. Following inoculation, fever (40.0° to 41.1°C) on the first, second, or third day was the first sign of endocarditis. The rise in temperature occurred the same day as the development of positive blood cultures in 4 animals, but preceded positive culture by 24 hours in 2 animals. No calf in either group had positive blood cultures for *S. aureus* without subsequent, lethal prosthetic valve endocarditis. All animals demonstrated a sharp elevation in temperature in the first few days, but the elevation did not persist in half the animals.

Despite fever and bacteremia, the animals appeared healthy and ate well. The white blood cell counts (WBC) of 7 calves prior to infection averaged 9,210 per cubic millimeter of blood (range, 5,500 to 12,400) using fifteen samples. The WBC of 6 calves with prosthetic valve endocarditis averaged 9,530 per cubic millimeter (range, 7,100 to 11,500) using seven samples. The signs of illness were poor feeding and lying with the head down. These signs correlated with a change in the prosthetic valve sounds from distinct clicks to a muffling-of-the-ball click in all animals at a mean time of 7 days. One animal had a systolic murmur. Echocardiography in 2 calves demonstrated limited excursion of the ball. Jugular venous distention appeared in the subsequent 2 to 4 days, followed by rapid deterioration of the animal's clinical status, characterized by fatigue and dyspnea. Four calves died, and 2 were killed in a moribund state at a mean of 10 days (10 to 15 days) after inoculation.

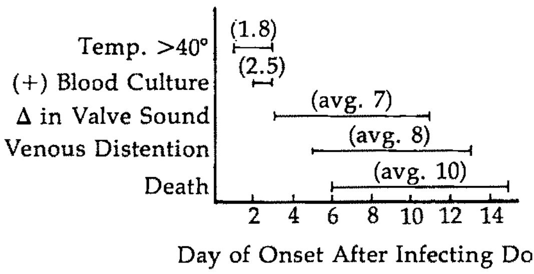

Fig 2. The day of onset of various signs and symptoms with the average day of occurrence shown for each clinical finding in 6 calves.

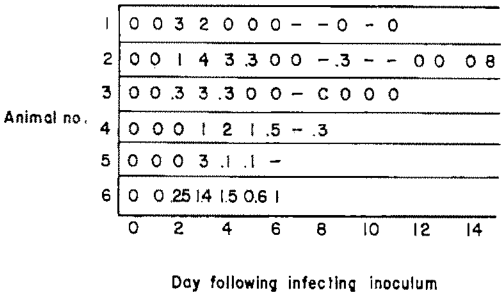

Fig 3. The culture results from four plates of 3 to 10 ml of jugular blood show the average number of organisms per milliliter of blood on each day after the infecting inoculum. (– = no culture; 0 = no growth.)

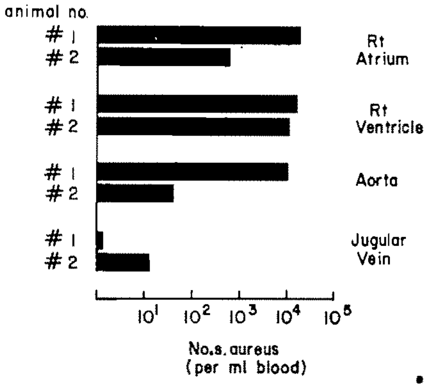

Fig 4. The bacterial concentration shown as the number (log) of organisms per milliliter of blood. Simultaneous cultures taken aseptically at the death of 2 moribund animals show heavily contaminated blood about the infected prosthesis with substantial clearing of bacteria before the jugular vein is reached.

Blood Culture Characteristics in Late Prosthetic Valve Endocarditis

The blood cultures of the animals with late tricuspid prosthetic valve endocarditis were all negative the first day after injection, but 66% were positive on the second day, and all were positive on the third day. Three of the 6 calves had negative blood cultures 5 or more days after the development of prosthetic valve endocarditis (Fig 3).

The positive jugular venous blood cultures from all 6 animals throughout the experiment averaged only 1.3 *S. aureus* organisms per milliliter of blood. After the first positive blood culture, seventeen of thirty-seven subsequent cultures were negative in 6 calves.

The finding of negative blood cultures in the presence of known infection prompted simultaneous culturing of multiple sites in 2 animals (Fig 4). The bacterial titer of jugular vein blood was low (1×10^1 and 1.7×10^1 per milliliter), but the right atrial bacterial titers were ten to ten thousand times greater (3.6×10^4 and 7.7×10^3 per milliliter). Right ventricular bacterial titers were similarly elevated (2.3×10^4 and 1.4×10^4 per milliliter), and corresponding aortic blood cultures varied (1.4×10^4 and 6.8×10^1 per milliliter).

Postmortem Findings in Late Prosthetic Valve Endocarditis

Postmortem examination of the prosthetic valve showed thrombus deposition on the valve which caused almost total occlusion of the valve orifice and immobilization of the poppet. Quantitative tissue cultures of the vegetations on the atrial and ventricular sides of the valve were essentially the same, with a mean of 10^9 *S. aureus* per gram of tissue. Histological slides with hematoxylin and eosin and Brown and Hopps stains showed clumps of colonies embedded in laminated layers of fibrin. These colonies did not appear to involve the interstices of the multistranded polyester fabric. The colonies in the deeper portion of the thrombus were larger, which is consistent with greater age.

Early Endocarditis

Endocarditis developed in 3 of 4 calves within 7 days after direct inoculation of 10^2 to 10^3 *S. aureus* into the prosthetic valve at operation. The clinical course, blood culture characteristics, and postmortem findings were similar to those in calves with late endocarditis.

Comment

Prosthetic valve endocarditis has been studied little in the animal model. Tricuspid valve replacement was shown by Bonchek and coworkers [3] to be technically easy to perform in the calf. Detmer and colleagues [5] demonstrated that an inoculum of 1×10^9 organisms of *S. aureus* injected into 8 calves three months after tricuspid valve replacement caused rapidly fatal prosthetic valve endocarditis. However, prophylactic antibiotics (penicillin and streptomycin) provided 100% protection from endocarditis. Calves without prosthetic valves tolerated an inoculum of 1×10^{11} organisms [5].

The present study augments the previous experiment by determining the minimum intravenous inoculum of *S. aureus* required to colonize an endothelialized tricuspid prosthetic valve. The work by Braunwald and Morrow [4] and our own observations indicate that tissue ingrowth and endothelialization of the cloth covering of the Cutter-Braunwald valve was complete two months after tricuspid valve replacement. The dose-response curve in this study was determined in the absence of prophylactic antibiotics. Prosthetic valve endocarditis developed in all animals but 1 after intravenous injection of greater than 10^7 *S. aureus* and in none with 10^6 organisms.

The natural history of acute *S. aureus* endocarditis of a tricuspid prosthetic valve was characterized in calves. The first evidence that the prosthetic valve was colonized was temperature elevation, which correlated with the development of positive blood cultures. These findings occurred on the second or third day after inoculation. However, persistent fever was not a constant finding in animals dying of prosthetic valve endocarditis. The temperature was taken once a day; hence, a sampling error may have occurred. A change in the auscultatory sounds of the prosthetic valve was usually associated with rapid deterioration of the animal. The clinical findings were suggestive of progressive prosthetic valve obstruction from thrombosis. This was confirmed at postmortem examination. The 6 calves died within 6 to 15 days after inoculation, a result similar to that previously reported [6]. Valve thrombosis was common in tricuspid valve endocarditis and has been demonstrated to be more frequent in late endocarditis of prosthetic mitral valves than in that of prosthetic aortic valves.

No animal had positive blood cultures on the first day after inoculation. Positive blood cultures represented prosthetic valve colonization in all instances. There was an incidence of 46% false negative blood cultures.

The average titer of all positive blood cultures drawn from the jugular vein was only 1.3 *S. aureus* organisms per milliliter of blood. One explanation of the low titer is the effective bacterial filtering by the pulmonary and peripheral capillary beds. Cultures taken from the right ventricle grew 10^4 *S. aureus* per milliliter of blood and simultaneous aortic titers were 1,000-fold lower in 1 animal. In the other animal, the peripheral capillary system removed 10,000 *S. aureus* organisms per milliliter of blood. These numbers indicate that bacterial titers are high in the blood that bathes a valve infected with 10^9 organisms per gram of tissue, but that the peripheral venous blood may be sterile. These data suggest that the sampling of atrial blood through a central catheter would give a higher probability of obtaining positive blood cultures in the presence of right-sided bacterial endocarditis. A previous clinical report indicated that there was little advantage in obtaining arterial or central venous blood cultures in comparison to peripheral venous sampling. However, these cultures were obtained from patients with left-sided endocarditis [2].

Death of the animal was due to dysfunction or thrombosis of the prosthesis. The absence of an overwhelming septicemia, as shown by the cultures, supports this conclusion. There were no deep-seated abscesses of the valve annulus as described for endocarditis of the aortic and mitral valve prosthesis. The lungs showed no septic emboli. Prevention of vegetation formation on infected natural valves has been accomplished in an experimental model by the use of warfarin; however, survival was shorter in anticoagulated animals [8]. The occurrence of hemorrhagic pulmonary infarcts with right-sided endocarditis and of central nervous system or systemic infarcts with left-sided endocarditis, has discouraged the use of warfarin.

The failure of SAH-treated valves to protect animals from late endocarditis may be related to leaching of the silver compound from the fabric. Antibacterial activity could not be detected in vitro from one SAH-treated prosthesis removed from a calf 60 days after implantation. Elution of silver was detectable in three valves. The antibacterial properties of the SAH treatment may be overwhelmed by large inoculums. Also, endothelialization of the sewing collar may act as an additional diffusion barrier to silver. There was an insufficient number of experiments to characterize the effectiveness of

SAH treatment of prosthetic heart valves in decreasing the incidence of operatively induced endocarditis.

The rapidity of progression of disease and death from valve thrombosis that occurred in this study demonstrates the urgency of early diagnosis and institution of appropriate therapy. Echocardiography, used in 2 animals to evaluate valve action, has potential value in evaluating prosthetic valve dysfunction associated with endocarditis. Emergency replacement of the infected prosthetic valve in these animals would have been required for survival.

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Management of Fusiform Ascending Aortic Aneurysms

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ABSTRACT **Thirteen patients had elective surgical treatment of fusiform ascending aortic aneurysms at Strong Memorial and Rochester General Hospitals from 1970 to 1978. There were 8 men and 5 women ranging in age from 51 to 78 years (mean, 61 years). Nine patients underwent composite tube graft and aortic valve replacement, 3 had aortic valve replacement plus supracoronary tube grafts, and 1 had aortic valve replacement plus aneurysmorrhaphy. Coronary reimplantation alone or combined with saphenous vein bypasses was fashioned in 10 patients. Potassium cardioplegia was considered a useful adjunct in 6 patients. Two early deaths accounted for an operative mortality of 15.4%. There were 3 late deaths. Eight patients are alive and well 2 to 109 months after operation.**

The management of fusiform ascending aortic aneurysms requires surgical repair to prevent aortic rupture or dissection, left ventricular failure secondary to aortic insufficiency, and displacement of vital structures [9]. This technically demanding operation has in the past decade been facilitated by the use of composite tube graft and aortic valve prostheses, by highly developed methods of coronary artery reconstruction, and by a strict attention to techniques of myocardial preservation. This review stresses the importance of these technical aspects in a series of patients undergoing elective repair of ascending aortic aneurysm.

Material and Methods

Thirteen patients with fusiform, nondissecting ascending aortic aneurysms underwent surgical treatment at Strong Memorial Hospital and Rochester General Hospital between 1970 and 1978. The 8 men and 5 women ranged in age from 51 to 78 years (mean, 61 years). Preoperative clinical findings were as follows: precordial murmurs of aortic insufficiency, all patients; a history of congestive heart failure, 9; chest pain, 8, but only 5 had pain typical of angina pectoris; musculoskeletal stigmata of Marfan's syndrome, 2; and hypertension, 2.

Admission chest roentgenograms of these individuals revealed one or more characteristic findings (Fig 1). The degree of cardiomegaly ranged from borderline to marked. Right hilar prominence of the aortic silhouette was noted in most of the patients. A few roentgenograms demonstrated congestive heart failure.

Preoperative angiograms defined the fusiform aneurysms accompanied by marked aortic regurgitation in all patients (Fig 2). However, selective coronary arteriography was completed in only 1 of the 5 patients with angina. Of the 3 patients with nonanginal chest pain, 2 had incomplete coronary arteriograms and 1 had no coronary study.

The patients were divided into four surgical groups. Seven patients (Group 1) received composite tube graft and aortic valve prostheses plus reimplantation of coronary ostia into side holes made in the tube grafts. Two patients (Group 2) received composite grafts and a combination of coronary ostium reimplantation plus aortocoronary artery bypass with reversed saphenous vein. Three patients (Group 3) underwent aortic valve replacement plus insertion of a supracoronary tube graft to reconstruct the ascending aorta. Group 4 includes 1 patient who had an aortic valve replacement plus aneurysmorraphy and double aortocoronary artery bypass.

Cardiopulmonary bypass was established in all patients by cannulas in the femoral artery and right atrium. The left ventricle was decompressed through the apex or right superior

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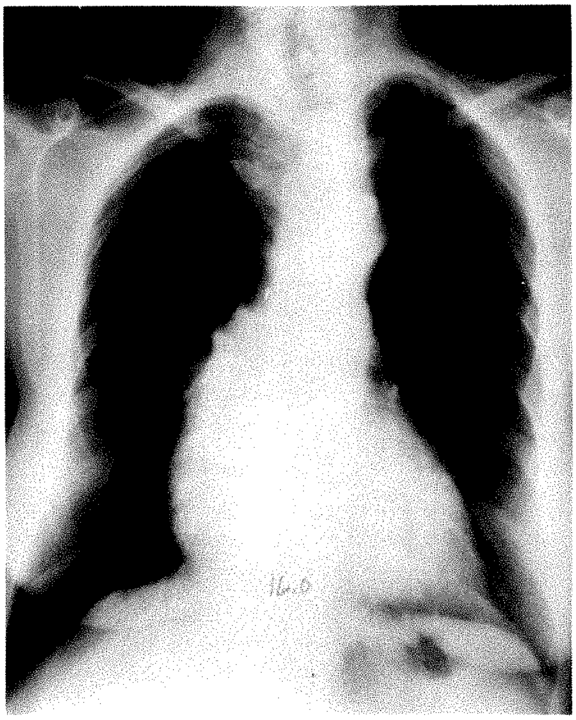

Fig 1. Posteroanterior chest roentgenogram showing prominent ascending aorta and cardiomegaly.

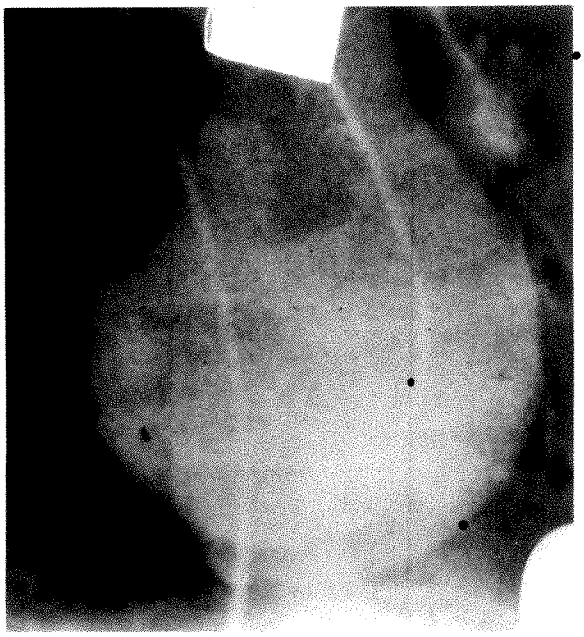

Fig 2. Posteroanterior thoracic aortogram showing marked pear-shaped dilatation of the ascending aorta.

Myocardial Preservation Techniques

Variables	Systemic Cooling	Coronary Perfusion	Potassium Cardioplegia
No. of patients	13	7	6
Dates of operation	2/70–11/78	2/70–4/77	8/76–11/78
Group 1	7	3	4
Group 2	2	0	2
Group 3	3	3	0
Group 4	1	1	0
Core temperature (°C)	20–30 (mean, 25.7)	24–28 (mean, 26.6)	20–30 (mean, 25)
Myocardial temperature (°C)	...	Not measured	Less than 20
Aortic clamp time (min)	...	45–177 (mean, 125.5)	71–140 (mean, 105.5)
Myocardial infarction	...	2	0
Operative deaths	...	2	0
Late deaths	...	3	0

pulmonary vein. All patients were cooled systemically to 20° to 30°C (mean, 25.7°C). Seven patients had direct coronary artery perfusion, and 6 had cold potassium cardioplegia (Table). In 2 patients in the latter group, myocardial temperatures were measured and were below 20°C while the aortas were clamped. The accumulated aortic cross-clamp times are summarized in the Table.

Twelve woven tube grafts were 25 to 35 mm in diameter. Six Starr-Edwards (sizes 9 to 12) and seven Lillehei-Kaster (sizes 16 to 25) valve prostheses were used; both types were incorporated in the composite grafts. The aneurysm wall was fashioned around the tube grafts in 8 patients, resected in 4, and imbricated for definitive repair in 1.

Figure 3 illustrates the insertion of the com-

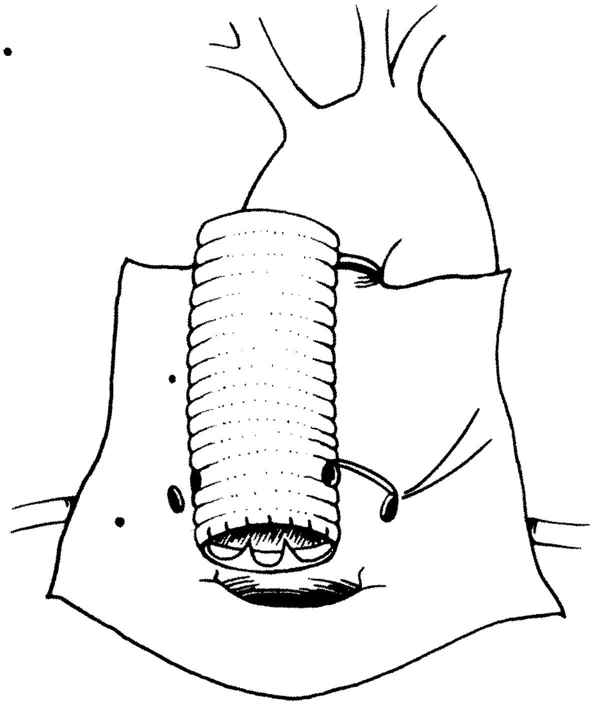

Fig 3. Insertion of the composite graft. Anastomosis of the Dacron tube to the coronary ostia with a running suture. The technique is begun after the prosthesis is sewn to the aortic annulus.

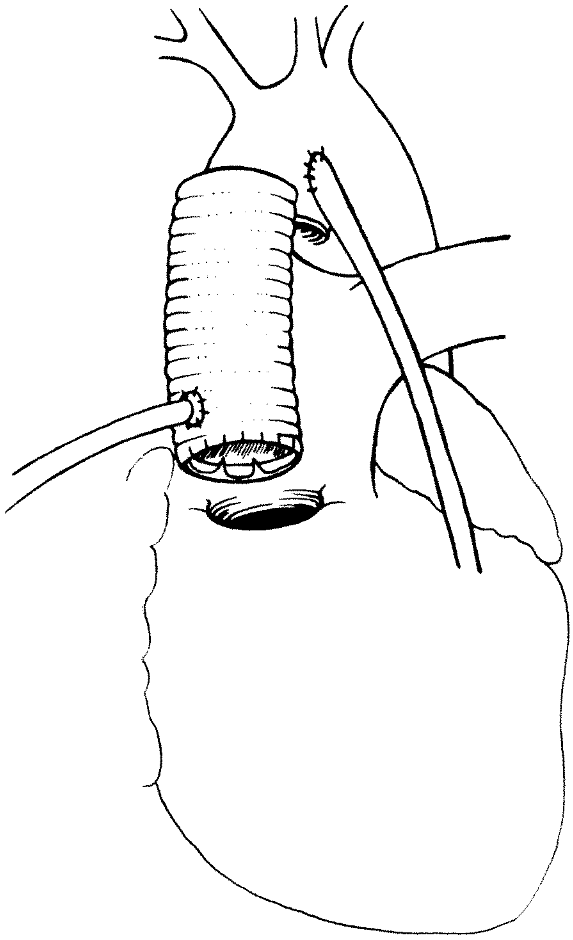

Fig 4. Anastomosis of the right coronary artery with a cuff of aorta to the Dacron tube. The vein graft is sewn to the aorta distal to the Dacron tube.

posite graft in Group 1. After the graft is sewn to the aortic annulus, the upwardly displaced coronary ostia are reimplanted into side holes in the Dacron tube, using a running 4-0 Prolene suture technique. The distal graft–aorta anastomosis can then be started inside the aorta to allow subsequent wraparound of the aneurysm wall to aid hemostasis.

In 1 patient in Group 2, the right coronary ostium was mobilized with a cuff of aorta and then reimplanted into the Dacron tube (Fig 4). The saphenous vein graft in this patient was brought off the aorta above the tube graft to minimize bleeding in the suture line.

Figures 5 and 6 illustrate the techniques used in Groups 3 and 4, respectively. In Group 3, Teflon strips were used, as popularized by Anagnostopoulos [1], to reinforce both the proximal and distal anastomoses between aorta and tube graft. Likewise in Group 4, Teflon strips reinforced the aortic closure. It is notable that the integrity of the aortic wall in the patient in Group 4 was sufficient not only to allow safe aneurysmorraphy but also to support aortocoronary bypass of the triple-vessel disease.

Pathology

Excised valve cusps were grossly deformed and had irregular, thickened areas. Nine of twelve valves examined histologically showed myxomatous changes. Six of eight specimens of aorta showed microscopic changes ranging from medial mucoid degeneration to cystic medial necrosis.

Results

Complications

Two patients required early reexploration for suture line bleeding. In 1 of them the bleeding was not controlled, and the patient died. Two patients sustained perioperative myocardial infarctions. One survived, and the other died of low cardiac output failure after a prolonged period. The operative mortality was 15.4%.

One patient had early malfunction of the

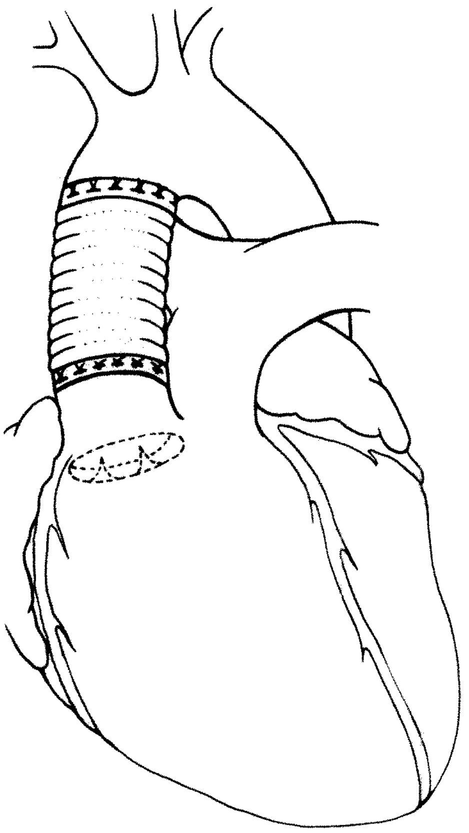

Fig 5. Supracoronary tube graft in Group 3 patients. Note the use of Teflon strips to reinforce the aortic suture lines.

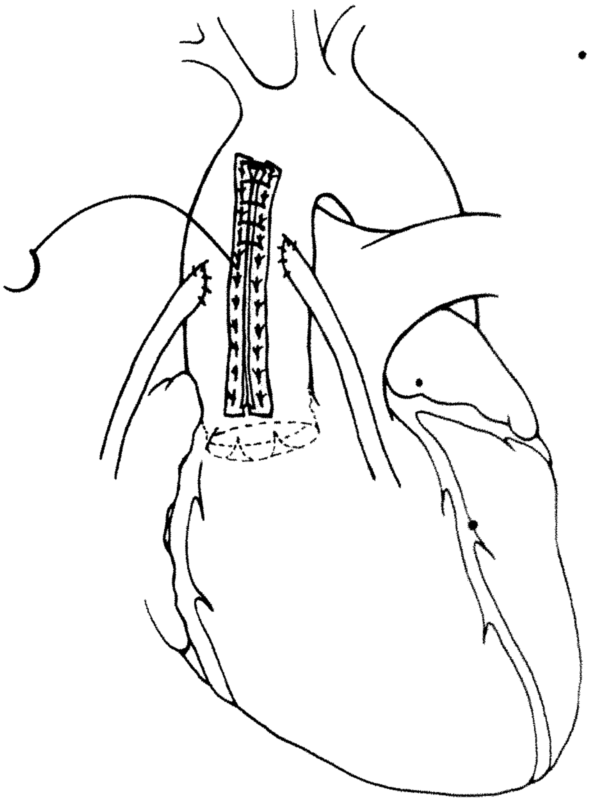

Fig 6. Use of Teflon strips to reinforce the closure of the aneurysmorrhaphy.

valve prosthesis, necessitating reoperation and rotation of the disc. Atrial fibrillation developed in 3 patients, and another had a transient heart block postoperatively. In 1 patient, respiratory insufficiency necessitated prolonged ventilator support. Another patient had mild leg ischemia related to femoral artery cannulation; no treatment was required.

Follow-up

Figure 7 depicts the follow-up of these patients. Three died of unknown causes 12, 21, and 31 months postoperatively. Therefore, 8 patients were alive and well from 2 to 109 months after operation. All 4 surgical groups are represented in these 8 survivors.

In 2 patients in Group 1, postoperative angiograms were made. One study showed good function of the composite graft. The left coronary artery was visualized, but the right was not. This patient died 21 months postoperatively. The second study also showed proper

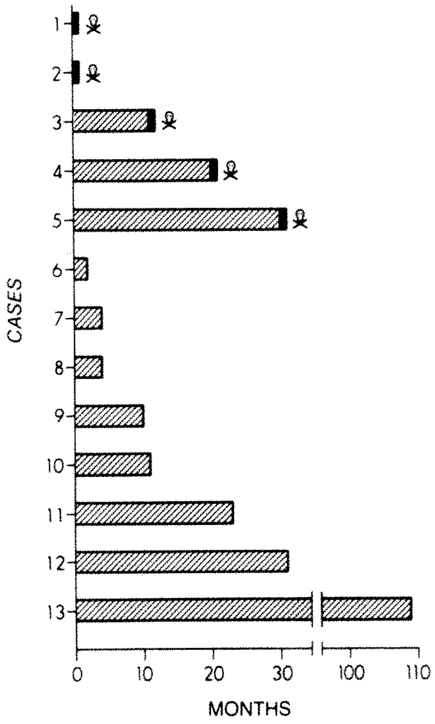

Fig 7. Patient follow-up: 8 patients are alive and doing well 2 to 109 months postoperatively.

composite graft function and visualization of both coronary arteries. This patient is doing well one year after operation. Neither angiogram revealed an anastomotic or perivalvular leak.

Comments

The low incidence of hypertension in these 13 patients is interesting. Up to 87% of patients with acute aortic dissections are hypertensive [12]. However, like those with aortic dissections, our patients had myxomatous valve degeneration and idiopathic aortic medionecrosis, as described by Davies [6]. Most of them seem to fit the so-called forme fruste pattern of Marfan's syndrome [5].

Evaluation of patients with fusiform ascending aortic aneurysms should include selective coronary angiography. However, massive dilatation of the aortic root with displacement of coronary ostia often makes this study difficult to complete.

The use of a composite graft to repair an ascending aortic aneurysm was applied by Bentall and DeBono [3] in 1968. Edwards and Kerr [7] proposed wrapping the aneurysm wall around the tube to facilitate hemostasis. The present series substantiates the applicability of these techniques, as do other recent reports [4, 10, 11]. However, the value of flexibility on the part of the surgeon and the ability to fashion the operation to the patient are also emphasized. The appropriate operation for these patients requires careful evaluation at operation of the extent of aneurysmal dilatation, displacement of coronary ostia, and, to a lesser extent, the gross integrity of the aortic wall. Furthermore, current techniques of coronary artery revascularization offer the surgeon useful alternatives for reconstituting coronary flow with repair of these aneurysms.

In the past two years, groups in Minneapolis, Pittsburgh, and London have advocated the use of cold cardioplegia for myocardial preservation during these operations [2, 4, 10]. In the current series there were no operative deaths or major complications in the cardioplegia group (see Table). One death secondary to myocardial infarction resulted from a left main coronary dissection caused by manipulation of the perfusion cannula. We believe that utilization of cold potassium cardioplegia can facilitate effective myocardial preservation in these patients during the aortic cross-clamp period. Infusion of the solution can be intermittent as needed to keep the myocardial temperature below 20°C and thus preclude the frustration of keeping coronary perfusion catheters in place.

As others [8, 10] also have pointed out, composite graft placement can be done with an acceptable mortality. However, more data are needed to predict the outcome of these patients beyond two to three years. Mayer and his group [10] stress the importance of postoperative angiograms. Because of the diffuse nature of the degenerative collagen disorder in these patients, the late occurrence of pseudoaneurysms and paravalvular leaks is not surprising.

Two of our late deaths occurred after composite graft placement. The early postoperative angiogram in 1 of these patients did not show visualization of the right coronary artery, but the death at 31 months was unexplained. The other patient died 12 months postoperatively, also of unknown cause. We agree that close follow-up with periodic angiograms in this patient population is necessary.

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CASE REPORTS

Blastomycosis of the Esophagus

Alim Khandekar, M.D., Davis Moser, M.D., and William J. Fidler, M.D.

ABSTRACT **A patient had clinical, endoscopic, and roentgenographic signs of esophageal carcinoma, but biopsies and brushings were negative. At operation he was found to have blastomycosis localized to the esophagogastric region and adjacent lymph nodes. There was no evidence of pulmonary disease. He was treated successfully by partial esophagectomy and amphotericin. The literature on esophageal blastomycosis is reviewed.**

The gastrointestinal tract is seldom the site of blastomycosis. When involvement occurs, it is usually part of widely disseminated disease. We report here an unusual case of blastomycosis in which the esophagus was the main site of involvement, apparently without pulmonary disease. The patient had typical clinical and roentgenographic signs of carcinoma. Relief of obstruction and diagnosis were obtained by operative resection.

A 42-year-old black man gave a six-week history of progressive dysphagia and a weight loss of 9 kg. He complained that solid food stuck in his throat and that he occasionally regurgitated food. He denied fever, chills, night sweats, cough, hematemesis, hemoptysis, or heart disease. There was no history of ingestion of corrosive liquids.

He was a farm worker in eastern Arkansas. He occasionally drank water from a shallow well and unpasteurized milk. He smoked a pack of cigarettes daily and drank alcohol in moderation. He was well developed, well nourished, and in no distress. There was slight tachycardia and slight dehydration. The remainder of the physical examination was unremarkable.

Admission hemogram and routine chemistry tests were unremarkable except for slight elevations of serum calcium and alkaline phosphatase, which returned to normal after hydration. The chest roentgenogram was normal except for scattered calcifications in the lungs and hilar regions. Hilar tomograms did not reveal node enlargement. An upper gastrointestinal study showed a constricting lesion in the lower third of the esophagus and some proximal dilatation (Fig 1). The esophagus was rigid in the lesion and had an irregular, spiculate mucosa. The roentgenograms were thought to be typical of esophageal carcinoma. Liver-spleen scan was normal. Bone scan and intravenous pyelogram were negative. Esophagogastroscopy on two occasions showed rigidity and narrowing of the distal esophagus with elevated white mucosa suggestive of neoplasm. Biopsies and brushings showed only mucosal hyperplasia. Bronchoscopy was normal.

It was elected to operate to establish a diagnosis and to perform an esophagogastrectomy if possible. Laparotomy through a midline incision was done. The gastric wall at the esophagogastric junction was markedly thickened; there were an enlarged node at the cardiac area and a nodule at the left border of the porta hepatis. Frozen section of the node showed granulomatous inflammation. Culture of the node is described later. The proximal stomach was opened, and biopsy sections were taken but showed only chronic inflammation without granulomas. Because of marked stricture and periesophageal fibrosis, it was thought that short-term dilation would be of little value. Therefore, the partial esophagogastrectomy was completed along with pyloroplasty and fundoplication. During dissection, the lower esophagus was seen to be markedly thickened but no tumor was found. Mediastinal lymph nodes were unremarkable.

The patient had an uneventful recovery and resumed normal alimentation within two weeks. Following definitive diagnosis, he was treated with a ten-week course of systemic amphotericin. The therapy was tolerated well. He

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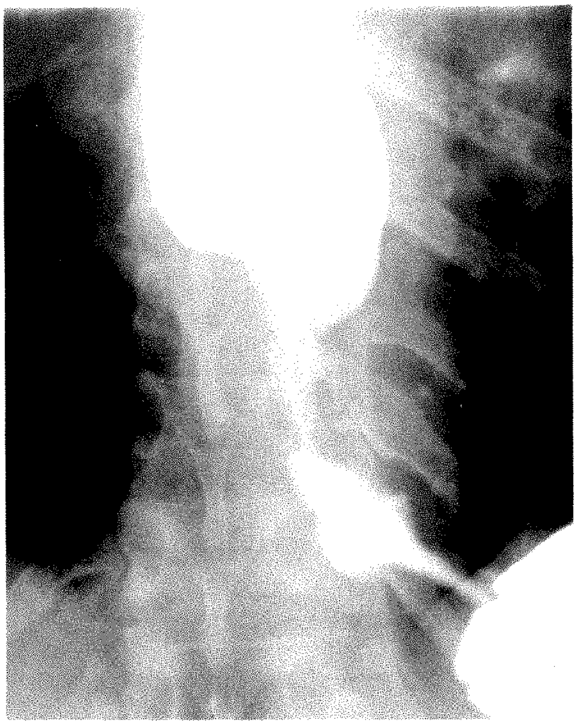

Fig 1. Barium swallow showing the distal constricting lesion.

regained his previous body weight and has a well-functioning gastroesophageal anastomosis thirteen months after operation.

Pathological Findings

There were necrotic granulomas in the distal esophagus and in celiac, perihepatic, and perigastric lymph nodes. The granulomas were characterized by epithelioid histiocytes, multinucleated giant cells, and central acute inflammation (Fig 2). Many of the giant cells contained large, thick-walled yeasts with single buds characteristic of *Blastomyces dermatitidis* (Fig 3). The esophageal wall was markedly thickened due to pseudoepitheliomatous hyperplasia, granulomatous inflammation, muscular hypertrophy, and fibrosis. The surgical margins were free from granulomas.

Part of the celiac lymph node was cultured on Sabauraud's dextrose agar and in ten days grew typical mycelial forms of *Blastomyces dermatitidis*. This was then transformed to the yeast phase on brain–heart infusion (BHI) blood agar. Fungal serological findings and cultures of sputum and urine were negative.

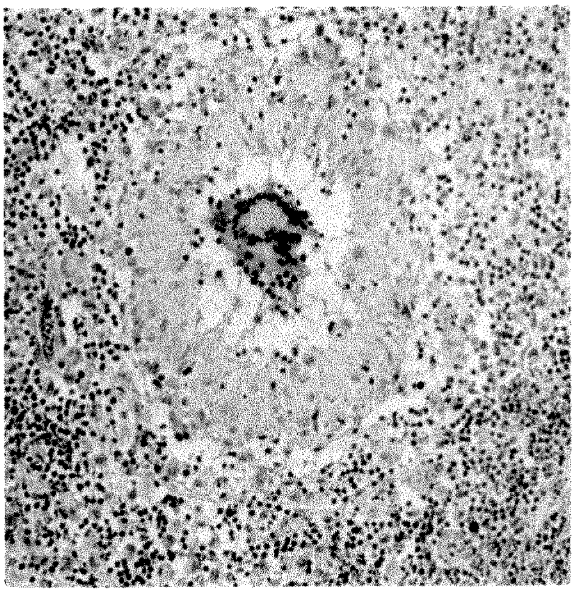

Fig 2. Granuloma with central giant cell in esophageal submucosa. (H&E; original magnification ×175.)

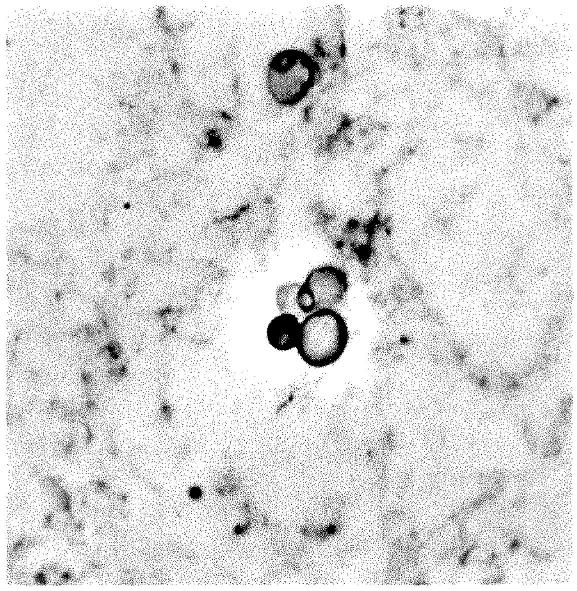

Fig 3. Typical Blastomyces *yeasts with single buds. (Gomori's methenamine silver; original magnification ×400.)*

Comment

North American blastomycosis commonly involves the lungs and skin and, less frequently, bones and genitourinary tract. Lesions in the gastrointestinal tract are so uncommon that the major textbook on gastroenterology mentions blastomycosis as one of the "clinical curiosities" of gastroenterology [5]. One review article [1] stated that "the gastrointestinal tract is spared in blastomycosis," and that this fact is useful in differential diagnosis from histoplasmosis and South American blastomycosis in which gastrointestinal lesions are relatively common. In most reviews of blastomycosis, gastrointestinal involvement was absent or was an incidental finding in disseminated disease. Documented esophageal involvement was found only in a few instances.

In 1911, Shepherd and Rhea [9] reported on a patient who had a 1 cm blastomycotic lesion in the middle part of the esophagus that was found at postmortem examination to be part of widely disseminated disease. The esophageal lesion apparently had caused no symptoms. One of 13 patients reported by Martin and Smith [6] had microscopically proved esophageal blastomycosis. At postmortem examination, the lesion was found to be part of a systemic infection. Cherniss and Waisbren [3] reported that among 40 patients, 2 had esophageal involvement. One had a bronchoesophageal fistula as a secondary complication of pulmonary disease. The other had dysphagia for four years before the onset of skin lesions. He did not have pulmonary involvement. In one of the largest series [2], only 1 of 198 patients had dysphagia as the presenting symptom, but details of that patient were not given.

Blastomycosis causing dysphagia has been reported in 2 other patients. One of them had tuberculosis and a stricture in the upper third of the esophagus [10]. Biopsy showed blastomycosis, and he was treated by dilation. There was no follow-up information. This patient also was mentioned in a later review of blastomycosis [4]. The other patient had dysphagia, a weight loss of 18 kg, and bilateral pulmonary infiltrates [8]. A stricture was found in the middle and upper esophagus. Biopsy of the esophagus was negative but a biopsy of the epiglottis showed blastomycosis, and *Blastomyces* was cultured from a neck abscess. Multiple courses of stilbamidine were given. After eleven months, cultures and biopsies were negative but the esophageal stricture remained.

Esophageal stricture due to *Candida* was reported and reviewed in 1978 [7]. The patient reported and most of those reviewed had strictures in the upper half of the esophagus. In the 3 patients with esophageal blastomycosis for whom adequate documentation of the site of the lesion was available, again the middle or upper esophagus was involved. Stricture of the esophagus in fungal disease may be associated with inflammation of the submucosal esophageal glands, which are more numerous in the upper esophagus [7].

Our patient was seen initially with dysphagia and weight loss. Endoscopic and barium swallow examinations revealed findings typical of carcinoma, but biopsy and brushings did not reveal the diagnosis. It is generally accepted that blastomycosis at nonpulmonary sites is the result of lymphatic or hematogenous spread from a primary pulmonary focus. In our patient, the pulmonary focus, if it existed, was inapparent as shown by negative chest roentgenograms, hilar tomograms, and sputum cultures, and absence of mediastinal node abnormalities at operation. Without pulmonary disease, virtually no consideration was given to the possibility that a fungal infection might have been responsible for the stricture. The esophagus and periesophageal tissues were so thick and rigid that it was thought that dilation would not have relieved the stricture. Therefore, the diagnosis of blastomycosis was established only by operative resection. The histological findings were remarkably similar to those seen in cutaneous blastomycosis—complete with marked "pseudoepitheliomatous" hyperplasia of the squamous epithelium. This unusual case is a reminder of how fungal disease can mimic neoplasm, both clinically and pathologically.

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Notice from the American Board of Thoracic Surgery

The American Board of Thoracic Surgery now requires that candidates pass both the written and oral portions of the certifying examination.

In 1980 and thereafter, a written examination will be given *prior* to the oral examination. It will be necessary to pass the written examination before the oral examination can be taken. The closing date for registration for 1981 is August 1, 1980. The exact times and places of these examinations will be announced later.

A candidate applying for admission to the 1981 certifying examination must fulfill all the requirements for the Board in force at the time the application is received.

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Surgical Technique in the Management of Patent Ductus Arteriosus in the Elderly Patient

John Bell-Thomson, M.D., Edward Jewell, M.D., F. Henry Ellis, Jr., M.D., Ph.D.,
and Jules R. Schwaber, M.D.

ABSTRACT **The successful surgical treatment of a patent ductus arteriosus in a 68-year-old man is presented. A review of current methods for repair is discussed, with emphasis on the simple and safe technique described here.**

Surgical closure of a patent ductus arteriosus is performed easily by conventional techniques and is associated with a low hospital mortality in infancy, childhood, or adolescence. In the adult, on the other hand, a patent ductus arteriosus can be complicated by pulmonary artery hypertension, aneurysmal dilatation of the duct with calcification, and chronic endarteritis resulting in friable tissues that increase surgical risk because of the possibility of operative hemorrhage.

Management of a patent ductus arteriosus in the elderly remains controversial. In a case report of a 56-year-old man, Luisada and Bhat [13] stated that lack of symptoms and advanced age precluded the need for surgical repair, and this view is shared by others [1, 4, 9]. On the other hand, in a review of 53 adults who underwent operation for patent ductus arteriosus at the Toronto General Hospital, Black and Goldman [2] stated that the presence of an isolated patent ductus arteriosus in the adult is not associated with major complications and that repair is possible with gratifying results and a low mortality. In this brief presentation of successful division of a patent ductus arteriosus in a 68-year-old man, we reemphasize the need for surgical repair, regardless of the patient's age, and describe a safe technique for its performance.

A 68-year-old man was known to have had a patent ductus arteriosus since childhood at which time a machinery-type murmur was first heard over the upper left sternal border. Surgical repair was suggested 19 years before admission. However, since the patient was asymptomatic, he refused operation. Symptoms of dyspnea on exertion first developed 8 years before admission, and cardiac catheterization was performed. The findings were interpreted as diagnostic of a patent ductus arteriosus with a 1.6 to 1 left-to-right shunt. Pulmonary artery pressures were 37/15 mm Hg, and pulmonary artery wedge pressure was 23 mm Hg. Cardiac output with exercise, as determined by the Fick method, disclosed a pulmonic flow of 21.1 L/min and a systemic flow of 12.9 L/min. Surgical repair again was advised but was refused.

Three months before admission the symptoms worsened, and the patient began to experience dyspnea during normal activities. When he was admitted to the hospital, physical examination revealed a thin man who appeared vigorous but who was in mild congestive heart failure with a classic machinery-type murmur heard best at the upper left sternal border. Thoracic roentgenography demonstrated cardiomegaly and pulmonary artery engorgement (Fig 1). Electrocardiography showed atrial fibrillation, left ventricular enlargement, and the effect of digitalis. Pulmonary function studies indicated severe obstructive and restrictive defects. Repeat cardiac catheterization revealed a pulmonary blood flow of 9.9 L/min, a systemic blood flow of 3.6 L/min, and a left-to-right shunt of 2.8 to 1. Pulmonary artery pressures were 70/42 mm Hg, pulmonary artery wedge pressure was 26 mm Hg, and pulmonary artery

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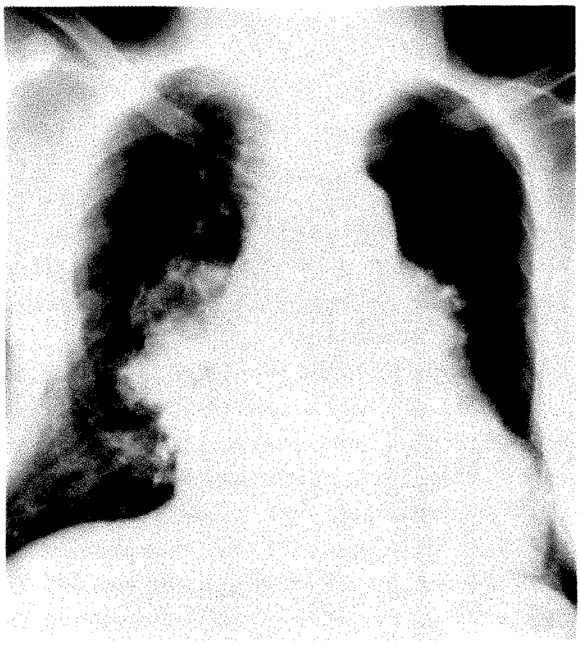

Fig 1. Posteroanterior thoracic roentgenogram made before operation demonstrating cardiomegaly and prominent pulmonary arteries.

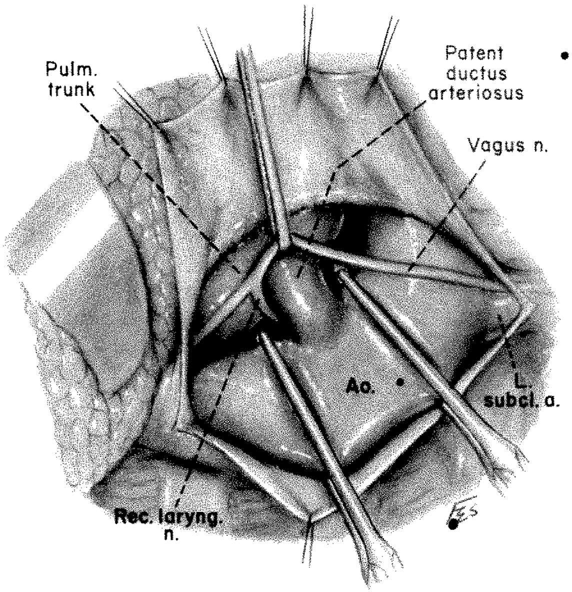

Fig 2. Technique of exposure of the patent ductus arteriosus with cross-clamping of the aorta.

resistance was calculated to be 2.8 dyne sec cm^{-5}. The pulmonic flow was 9.1 L/min at rest and 10.7 L/min with exercise. The systemic blood flow was 2.5 L/min at rest and 2.9 L/min with exercise.

The patient underwent surgical division of the patent ductus arteriosus and made an uneventful postoperative recovery. Convalescence was complicated by urinary retention and overflow incontinence for which transurethral resection of the prostate was required. Subsequently, he was discharged without symptoms.

Technique

The surgical technique used in this patient has been described previously [5, 7, 11]. The patient is placed in a right lateral decubitus position for a left posterolateral thoracotomy, and the incision is made through the bed of the nonresected fifth rib. The parietal pleura is incised over the aorta and reflected medially, with care taken to identify the vagus nerve and the recurrent nerve as it partially encircles the patent ductus. The aorta above the ductus is encircled with tape as is the descending thoracic aorta below the ductus. Dissection is continued to identify the ductus, which is encircled with a No. 1 silk suture. The aorta is cross-clamped above and below the patent ductus arteriosus (Fig 2), and, while arterial pressure is monitored with a right radial artery line, sodium nitroprusside is infused to maintain a systolic pressure below 160 mm Hg. A third vascular clamp is applied on the ductus itself. This must be done carefully so as not to include the pulmonary artery within the confines of this clamp. The ductus is divided at its aortic end, including a small rim of aortic wall. The aorta is closed with a running 4-0 vascular suture, and the cross-clamps are removed (Fig 3). Attention is turned to the ductus, and the aortic tissue removed when the ductus was divided is oversewn with a running 4-0 vascular suture, after which the clamp occluding the ductus is released. The incision is closed in the usual manner, leaving a No. 28 chest tube in the pleural space. The tube is brought out through a separate incision in the skin.

Comment

The presence of a patent ductus arteriosus in the elderly is rare. In an excellent review of the natural history of patent ductus arteriosus, Campbell [3] showed that by the age of 30 years, about 20% of patients with this condi-

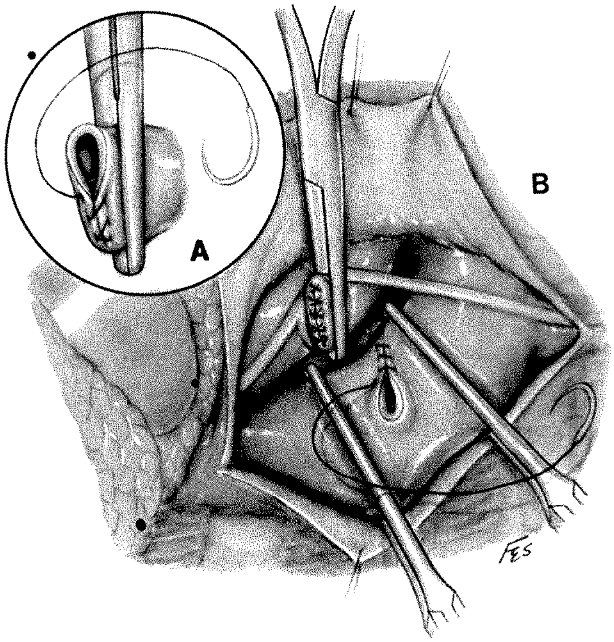

Fig 3. (A) Aortic end of the ductus after division at the beginning of the two-layer closure. (B) Completed two-layer closure of the aortic end of the ductus. The opening in the aorta is closed similarly.

tion will have died. From the fourth decade onward, mortality rises from 2.5% to 4% a year by age 60. After the age of 60 years, about 10% of the remaining patients will have died.

The surgical management of patent ductus arteriosus in the elderly can be complicated by the presence of aneurysmal dilatation of the duct, calcification, pulmonary artery hypertension, endarteritis, and friability, especially of a large, tense pulmonary artery. The complication most feared at the time of operation is hemorrhage from the pulmonary artery side of the ductus. We believe that with careful dissection and control of the aorta, both above and below the ductus, a vascular clamp can be applied safely to the aortic end of the ductus and the division performed through the aortic tissues, which allow for a secure closure on both sides without undue risk of bleeding. The use of sodium nitroprusside is advocated to prevent severe hypertension proximal to the aortic cross-clamp. It is recommended that the cross-clamps not be applied for any longer than fifteen minutes (as established by Crafoord and Nylin [5]), which we consider to be ample time to close the aortotomy.

Techniques employing total cardiopulmonary bypass or left heart bypass have been described [6, 14]. Robinson and associates [16] used deep hypothermia and circulatory arrest in treating adult patients. Laustela and associates [12] used a Teflon-pledgeted suture ligation technique with left heart bypass. Erdman and associates [8] used a similar suture ligation technique but added the use of induced systemic hypotension during dissection and ligature, as did Black and Goldman [2]. Taira and Akita [17] described a method using a patch mounted on a Fogarty catheter, which, with cardiopulmonary bypass, is inserted through the pulmonary artery; closure is undertaken from the pulmonary artery side. Thomas and associates [18] described a technique wherein a Potts-Smith clamp is applied to the aorta, which was previously encircled with Teflon felt. A curved vascular clamp is applied to the pulmonary artery, and the ductus is divided and closed with interrupted vascular sutures. The Teflon suture around the aorta is used to buttress the aortic closure. A shunt from the left subclavian to the descending thoracic aorta was used by Pifarré and associates [15] before cross-clamping the aorta above and below the ductus. After a third clamp was placed on the ductus itself, the aorta was opened and the ductus patched from the aortic side.

In our review of the literature to date, we found that the oldest male patient to survive surgical repair was 55 years of age, as reported by Robinson and associates [16], and the oldest female patient was 72 years of age, as reported by Hornsten and associates [10]. Our patient was 68 years old and is apparently the oldest man to undergo successful surgical division of a patent ductus arteriosus.

Editor's Note

Some surgeons believe that if the duct is calcified and if a tear of either side ensues, the surgeon is in an untenable situation. The use of cardiopulmonary bypass, draining the blood from the right pulmonary outflow tract and splitting the arterial inflow between the cannula in the transverse aortic arch and the femoral artery, is preferable in this situation.

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Coronary Artery Bypass Grafting: Simplification and Refinement of Surgical Technique

Ellis L. Jones, M.D.

ABSTRACT **Recent advances in technique and myocardial preservation that I have used in performing the coronary bypass operation are described. Rigid adherence to basic microsuture technique and use of hypothermic hyperosmolar cardioplegic solution and wide-field optical magnification have been responsible for improving graft patency rates and markedly reducing operative mortality during the past six years. With these techniques, hospital mortality has been 0.6% (3 deaths) in the last 500 consecutive coronary bypass operations.**

In recent years there has been a progressive decrease in surgical mortality with the coronary bypass operation. This is primarily due to refined surgical technique and improved myocardial preservation. The techniques to be described have been developed by me during the past six years in more than 1,500 surgical patients and are considered to be instrumental in improving graft patency and reducing hospital mortality.

Method

Partial cardiopulmonary bypass has been used in all patients with moderate systemic hypothermia to 28°C by esophageal measurement. The left ventricle is vented in all patients. Venting reduces ventricular wall tension and end-diastolic pressure during the operative procedure, thereby minimizing left ventricular dysfunction and backbleeding through the arteriotomy.

To minimize the risk of aortic dissection, cannulation of the ascending aorta is performed with a nonclamping technique (Fig 1). Venous cannulation is accomplished by a single atrial pickup only for single or double bypass grafts to the left anterior descending (LAD) and right coronary arteries. Separate caval cannulation slows premature warming of the right side of the ventricular septum.

Once the heart has cooled and spontaneously fibrillated, the coronary artery is dissected from its epicardial sheath. Dissection should be kept at a minimum, and only the anterior portion of the artery is freed from surrounding epicardial tissues. Limited dissection prevents subsequent elevation and angulation of the artery from its vascular bed. Incorporation of the lateral epicardial attachments (especially for small arteries) into the suture line adds strength and decreases the incidence of arterial wall tearing. Optical magnification is mandatory for precise placement of sutures, and a modified 3.5 power loupe* gives wide-angle magnification while retaining adequate depth of field.

Myocardial Preservation

Before the aorta is cross-clamped, pump flow is reduced to decrease wall tension and injury to the aortic intima. A modified Fogarty-Hydragrip clamp with two soft rubber inserts is placed across the aorta through the transverse sinus. If the aorta is noted to be extremely thin and soft, a commitment should be made to do the proximal anastomoses using total aortic occlusion to avoid producing aortic dissection or tearing.

A cold hyperosmolar solution is introduced through a No. 16 Silastic catheter placed in the ascending aorta to produce a homogeneous reduction in myocardial temperature. The concentration of the solution is as follows: potassium, 28 mEq/L; the bicarbonate radical, 9.3 mEq/L; sodium, 95.7 mEq/L; 50% dextrose, 3.2 ml; 15% mannitol, 200 ml; sterile water to 1,000 ml; pH, 8.1; and osmolarity, 415 mOsm at room temperature. (Myocardial cooling using a pericardial well of cold saline solution has not

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*Designs for Vision, New York, NY.

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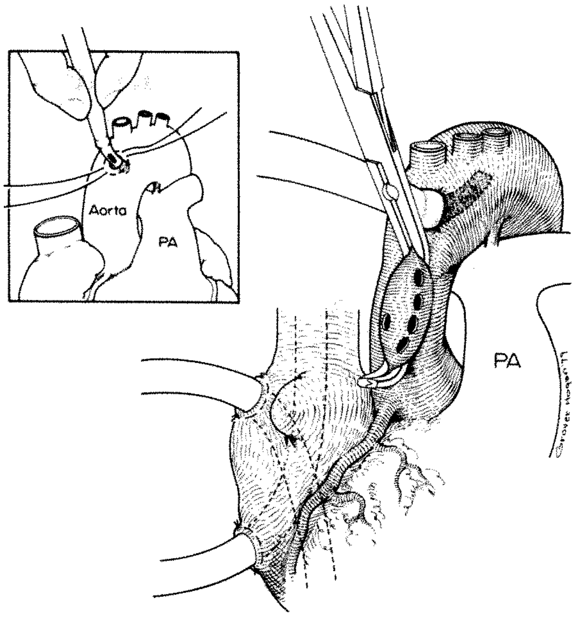

Fig 1. Application of an aortic clamp for proximal anastomoses, and demonstration of the aortic cannulation technique (inset). (PA = *pulmonary artery.)*

been employed because, during much of the operation, the heart is either elevated out of the pericardium or resting on a pad.) Four hundred fifty to 500 ml of this solution at 4°C is taken directly from the refrigerator and injected into the aorta. The potassium concentration of the solution has been periodically adjusted to achieve a current concentration that produces rapid electromechanical dissociation and cardiac arrest with minimal incidence of residual complete heart block following operation. The Pall Ultipor filter system has been used recently to eliminate the possibility of injecting microscopic particles of lint, air, or foreign material into the coronary arteries.

Although cardiac arrest usually occurs after several hundred cubic centimeters of solution have been introduced, an additional 200 ml are injected to decrease myocardial temperature well below 20°C. The effectiveness of perfusion hypothermia depends on the volume and temperature of the solution, aortic valve competency, and the absence of major noncoronary collateral vessels, which produce rapid clearing of the solution from the coronary vascular bed. Asanguineous hypothermic perfusion has been preferred to sanguineous perfusion because of greater simplicity, its capacity to operate at lower myocardial temperatures without increased viscosity, and the availability of a coronary vascular bed free from formed elements.

After the myocardium has become flaccid, a small arteriotomy is made with a Beaver M-75 blade. Care must be taken not to injure the posterior arterial wall. The incision is extended with small vascular scissors. Triangular wedges are not removed from the anterior surface of the artery because this could cause shattering of the arterial wall in patients with multilayered diseased vessels. If troublesome bleeding from noncoronary collaterals occurs, it can be satisfactorily controlled by placing the second assistant's finger over the proximal coronary artery (all arteries) or compressing the heart over a folded pad placed beneath the heart and lying in the interventricular groove (the LAD artery). A small suction tip catheter is used for removing the usual flow of blood through the arteriotomy site. Miniature T-shaped balloons [2] have not been necessary and are difficult to use in the smaller coronary arteries. To facilitate the right coronary artery anastomosis, which can be difficult distal to the posterior descending branch, the second assistant invaginates the right ventricular body with his hand, thereby elevating the distal right coronary artery into view. A simple white photographer's glove improves traction on the heart. Placing the patient in moderate Trendelenburg position also improves visibility in this area.

Locating the intramyocardial LAD is facilitated by following the anterior epicardial groove proximally and dissecting beneath this point. It also can be localized by following the diagonal branch proximally to its junction with the LAD. The LAD is then followed into the muscle until an undiseased segment is found. Care must be taken not to dissect too deeply to the right of the septum and enter the right ventricular cavity. Closure of the perforation may be difficult without compromising the circulation of the LAD. Exposure of this deep-lying structure is made easier if a small retractor of special design is used (Fig 2)*.

*Alm Minor Retractor, V. Mueller, Chicago, IL.

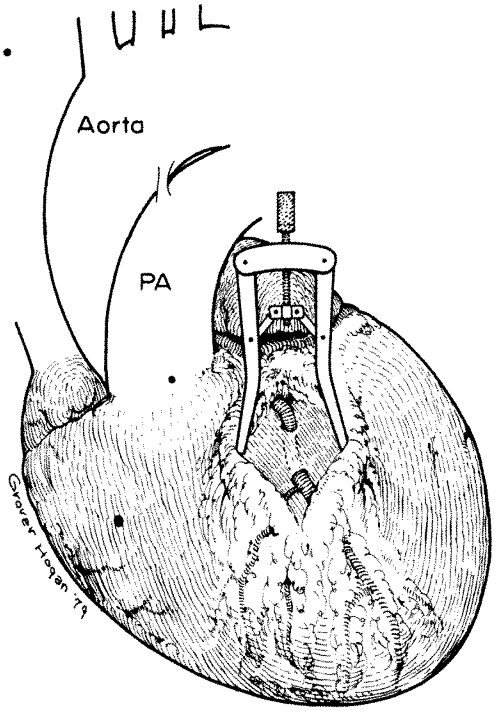

Fig 2. Exposure of the intramyocardial left anterior descending coronary artery. (PA = *pulmonary artery.)*

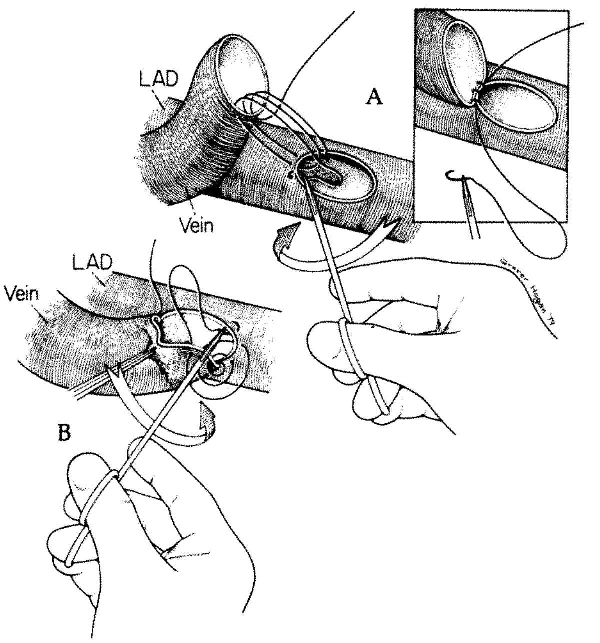

Fig 3. (A) Initial placement of sutures for distal anastomosis. (B) Suture placement in the toe of the anastomosis to facilitate exposure. (LAD = *left anterior descending coronary artery.)*

Anastomotic Technique

Once the arteriotomy has been made and the distal vein tailored to the proper angle, a continuous three-point suture of 7-0 Prolene initiates the anastomosis. The three sutures are placed in the "heel" of the artery and vein before the graft is lowered (Fig 3). For anastomoses performed to the right coronary, LAD, and diagonal arteries, the three apex sutures between the vein and artery are done in a backhanded fashion, and each bite into the artery is made slightly more superficial than the lateral wall sutures (see Fig 3). This approach opens up the anastomosis at the critical "toe" and avoids the pinching effect often seen in postoperative arteriograms or postmortem specimens [1]. Sequential grafts are easily performed using this technique, and greater flexibility is obtained if the side-to-side anastomosis is performed prior to the end-to-side anastomosis (Fig 4).

All distal anastomoses are performed first under one aortic cross-clamp. Multiple periods of cross-clamping are not only injurious to the ascending aorta, but may also increase myocardial and endothelial cellular edema [3]. Sys-

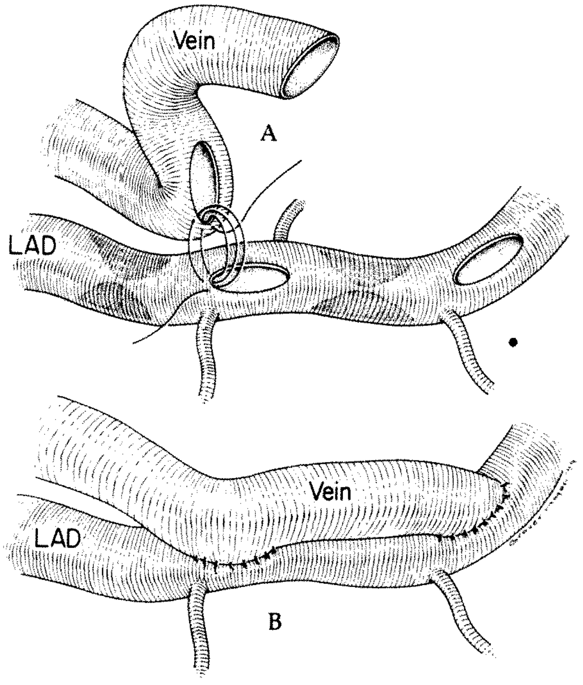

Fig 4. Sequential graft to the left anterior descending coronary artery (LAD).

temic rewarming is begun just prior to beginning the last distal anastomosis.

For the proximal anastomoses, a large side-biting clamp is placed well posterior on the ascending aorta. A stainless steel aortic punch with disposable circular blades has been used for removing a clean symmetrical segment of tissue from the aortic wall. Multiple grafts can be placed on the ascending aorta with a single application of the clamp, thereby minimizing the chance of aortic injury. Grafts are positioned along the aorta linearly, and as many as six can be placed comfortably along both sides of the aorta (see Fig 1). A 5-0 Prolene suture is used to perform the proximal anastomoses, done with a technique similar to the distal artery anastomoses. The appropriate length of vein graft is determined by temporarily retarding the venous line to expand the pulmonary artery and right ventricular outflow tract. This simulates the expanded heart and prevents gross disproportions in vein length. If a venous valve lies within several centimeters of the distal anastomosis, the arc of the graft should be reduced to avoid "buckling" and angulation at this location. Finally, air is evacuated from the grafts, the left ventricular vent is removed, and the patient is weaned from cardiopulmonary bypass. With these techniques, graft patency rates have been approximately 90% and hospital mortality has been 0.6% (3 deaths) in the last 500 consecutive coronary bypass operations.

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Notice from the American Board of Thoracic Surgery

The American Board of Thoracic Surgery will give a voluntary recertification examination in the fall of 1981. Diplomates interested in participating in this examination should maintain a documented list of their cardiothoracic operations performed two years prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings and other continuing medical education activities for the two years prior to application for recertification.

Some time during the summer, a Recertification Brochure will be mailed to all diplomates outlining the rules and requirements established for recertification in thoracic surgery. This brochure will also contain information about applying for the voluntary recertification examination.

Please address all communications to the American Board of Thoracic Surgery, 14640 E Seven Mile Rd, Detroit, MI 48205.

Single Catheter Technique for Cardioplegia and Venting during Coronary Artery Bypass Grafting

Neal W. Salomon, M.D., and Jack G. Copeland, M.D.

ABSTRACT **Two areas of current controversy concerning coronary artery bypass operations involve the use of cardioplegia and the need for left ventricular venting. We wish to describe a very simple, safe, and effective method of accomplishing both cardioplegic arrest and venting using a single 14-gauge catheter inserted into the aortic root.**

The use of chemical cardioplegia agents has gained widespread application for the rapid induction of flaccid diastolic cardiac arrest. Numerous solutions of widely varying chemical composition have been and are being used. Most utilize potassium chloride (10 to 40 mEq per 500 ml), hypothermia, and controlled pH and osmolality. Advantages of chemically induced cardioplegia include rapid production of arrest to avoid myocardial substrate depletion, central cardiac hypothermia to diminish myocardial metabolism, hyperosmolality to reduce obligatory edema secondary to ischemia, and delivery of aerobic or anaerobic substrate [1]. Many techniques have been devised for the delivery of cardioplegic solutions but most have in common either an intermittent or continuous infusion under pressure into the aortic root.

A separate consideration in coronary artery operations involves the physiological and technical aspects of left heart venting during the period of either aortic occlusion or coronary perfusion after ischemia. Advantages of venting include prevention of left ventricular distention, reduction of transmyocardial wall tension, and creation of a bloodless operative field; in general, it allows for enhanced subendocardial perfusion [2].

The major risk involved with venting is the introduction of air into the left-sided circulation. Appropriate precautions must be taken to avoid air embolization. In addition, if the beneficial physiological effects of left heart venting are accepted, the actual need for venting varies with the particular method of intraoperative myocardial protection used. For example, there is probably less indication to vent when cardioplegic arrest is utilized compared with intermittent ischemic arrest.

We have adopted a very simple method which involves using a single catheter for both infusion of cardioplegia and left heart decompression. A 14 gauge angiocatheter (Quik-Cath)* is inserted into the most superior aspect of the ascending aorta just prior to the initiation of cardiopulmonary bypass. Once on bypass, 500 ml of cardioplegic solution (0.9% normal saline solution at 3° to 4°C, containing 25 mEq of potassium chloride, buffered to pH 7.7, with osmolality adjusted to 370 mOsm) is infused through this catheter into the aortic root, and the ascending aorta just distal to the catheter is occluded progressively. The proximal aortic root is palpated for turgor in order to be certain that the solution is not infusing through the aortic valve and into the left ventricle. The solution is infused using a pressurized infusion bag inflated to 300 mm Hg. The entire infusion time is approximately 2 to 3 minutes.

Once the heart has arrested, the ascending aorta is completely cross-clamped and the same 14-gauge catheter is converted to a left-sided decompressing vent. The end of the infusion line, which was previously attached to the pressure bag, is simply lowered below table level and inserted into the inlet valve of the bubble oxygenator (Figure). The line then drains by the gravity siphon effect. The aortic valve remains incompetent, and with the catheter tip positioned in the aortic root, the left side will remain completely decompressed. The average

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*Travenol Laboratories, Vicra Division, Dallas, TX.

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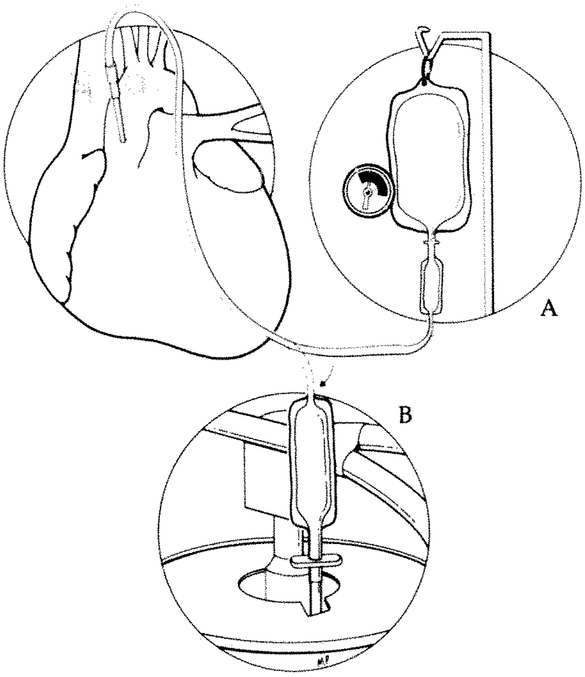

Single catheter technique: (A) Pressure infusion of the cardioplegic solution into the aortic root; (B) dependent gravity drainage venting the left heart through the aorta into the pump oxygenator.

rate of flow through this vent line is 50 to 60 ml per minute at bypass flow rates of 3 to 4 liters per minute. The gravity drainage is continued for the duration of the aortic cross-clamping period while the distal anastomoses are performed. Following removal of the aortic crossclamp, the catheter is removed and the vent site oversewn. The proximal aortosaphenous anastomoses are then performed. Profound topical cooling with continuous iced saline pericardial lavage is utilized for the duration of the aortic cross-clamp period.

The main risk with this technique is the introduction of air into the aorta. Air can enter through the open proximal coronary artery if the vessel is not totally occluded, either by a lesion in the native artery or by vessel occluders. If air enters during the period of aortic crossclamping, the siphon effect will be broken and the venting may become discontinuous. Systemic air embolization is very unlikely if the catheter is removed prior to unclamping, for the hole then serves as an air vent.

We have found this simple method to be completely safe and particularly valuable in patients with left ventricular hypertrophy and severe coronary disease associated with increased noncoronary collateral flow. The latter situation tends to diminish the efficacy of cardioplegia due to increased washout of cardioplegic solution and results in more rapid subendocardial warming. The technique has been used in approximately 50 patients and has been associated with no complications. Although no adequate control group has been evaluated, we have been impressed with the early postoperative results and lack of necessity for inotropic support.

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Combined Median Sternotomy and Posterior Lateral Thoracotomy: A Method for Proximal and Distal Thoracic Aortic Exposure

Thomas E. Williams, Jr., M.D., and James W. Kilman, M.D.

ABSTRACT **A method for exposure of the heart, ascending aorta, aortic arch vessels, and descending thoracic aorta in a single surgical field is presented. Five illustrative cases are reviewed. Indications for use include trauma to the aorta and arch vessels, aneurysms or dissections, ductus aneurysms, or complex or secondary coarctations of the aorta.**

In rare instances, extensive size or technical considerations can require exposure of the entire thoracic aorta. The use of combined median sternotomy and left posterolateral thoracotomy in the surgical treatment of 5 such patients has afforded adequate exposure, increased safety, and acceptable morbidity.

Case Reports

Patient 1

A boy born September 19, 1973, underwent extrapleural ligation of a patent ductus arteriosus on January 26, 1974. A subsequent chest roentgenogram showed enlargement of the mediastinum, and the diagnosis of a recannulated ductus arteriosus was established at cardiac catheterization (Fig 1). On May 17, 1974, the 4,490 gm child underwent reclosure of the ductus through a combined median sternotomy and left posterolateral thoracotomy through the fourth interspace. The vascular structures were isolated through the left chest; the right atrial appendage and ascending aorta were cannulated for cardiopulmonary bypass. The ductus aneurysm was then reclosed, using profound hypothermia and total circulatory arrest. On rewarming, the baby's heart started spontaneously, and a satisfactory cardiac output developed. Postoperatively, the child was supported with a ventilator for five days. The remainder of his convalescence was benign.

Patient 2

A 67-year-old man was awakened from sleep in April, 1974, with severe pain in the back and right shoulder. In August, 1974, a large aortic aneurysm was identified on chest roentgenogram (Fig 2). The patient was transferred to the Ohio State University Hospitals where an aortogram showed the aneurysm to be an old dissection extending from the level of the left subclavian artery to the diaphragm. On August 26, exploration was accomplished by means of a median sternotomy and posterolateral thoracotomy through the bed of the resected sixth rib, with posterior transection of ribs five and four. Control of the ascending aorta was gained through the anterior incision, and the aneurysm was isolated in the left chest proximal to the left subclavian artery and at the diaphragm. A Gott shunt was placed in the proximal aortic arch and inserted in retrograde fashion into the left external iliac artery. The aneurysm was repaired using a 35 mm woven Dacron prosthesis. The vessel wall was closed over the graft. Postoperatively, the patient had to be supported with a ventilator overnight. During the remainder of his convalescence, he showed steady improvement and was discharged on the thirty-seventh postoperative day.

Patient 3

A 49-year-old man was found to have an enlarging aneurysm of the aortic arch (Fig 3). On January 3, 1975, repair was attempted through a combined median sternotomy and left posterolateral thoracotomy through the bed of the resected sixth rib, as in Patient 2. The arch ves-

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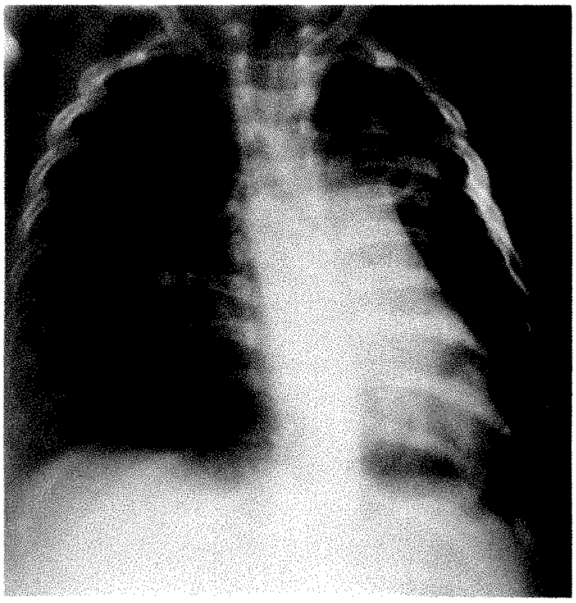


Fig 1. (Patient 1.) Posteroanterior roentgenogram before repair of the ductus aneurysm.

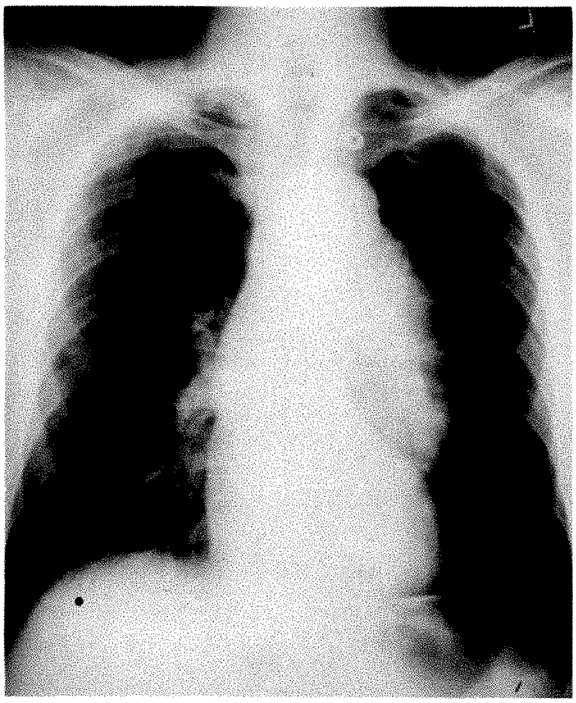


Fig 2. (Patient 2.) Posteroanterior roentgenogram before repair of the aortic aneurysm.

sels were isolated through the anterior incision. The descending aorta was isolated below the level of the aneurysm, which extended a hand's breadth below the left subclavian artery. A woven Cooley aortic arch prosthesis was sewn to the descending thoracic aorta. This was then passed anterior to the hilum of the lung into the sternotomy incision. The left subclavian artery, left common carotid artery, and innominate artery were serially detached and anastomosed to the three branches of the arch graft. For cardiopulmonary bypass, cannulas were introduced through the right atrium and left external iliac artery. After bypass was balanced, the descending aorta was cross-clamped above the level of the graft anastomosis, and the brachiocephalic vessels were perfused retrograde through the arch graft. The aneurysm was opened, and the proximal end of the prosthesis was sewn to the aortic root just above the sinuses of Valsalva. When the anastomosis had been completed, the graft was divided at the site of the anastomosis to the descending aorta, and the aneurysm was opened in the left chest. The graft was passed through the aneurysm and the distal end of the graft was anastomosed, end-to-end, to the descending aorta at its neck with the aneurysm. Cardiopulmonary bypass was terminated, and the patient supported a good cardiac output, but hemorrhage could not be controlled. Death ensued from what appeared to be a dissection of the aortic root with impairment of the blood supply to the right ventricle.

Patient 4

A 67-year-old woman was seen with a history of previous chest trauma and the roentgenographic findings of a mediastinal mass. Aortograms showed a huge aneurysm of the aortic arch (Fig 4). On December 29, 1977, repair was carried out through a combined median sternotomy and left posterolateral thoracotomy. Control was gained anteriorly through the median sternotomy and posteriorly by the thoracotomy. The patient was attached to cardiopulmonary bypass equipment and cooled to 18°C. Under these conditions of profound hypothermia and total circulatory arrest, clamps were applied and the aneurysm was opened through the left chest. An 8 × 3 cm patch was sewn to the inferior surface of the aortic arch to close the existing rent. The pump was turned back on and the field filled. Thereafter, the patient was rewarmed, and bypass was discon-

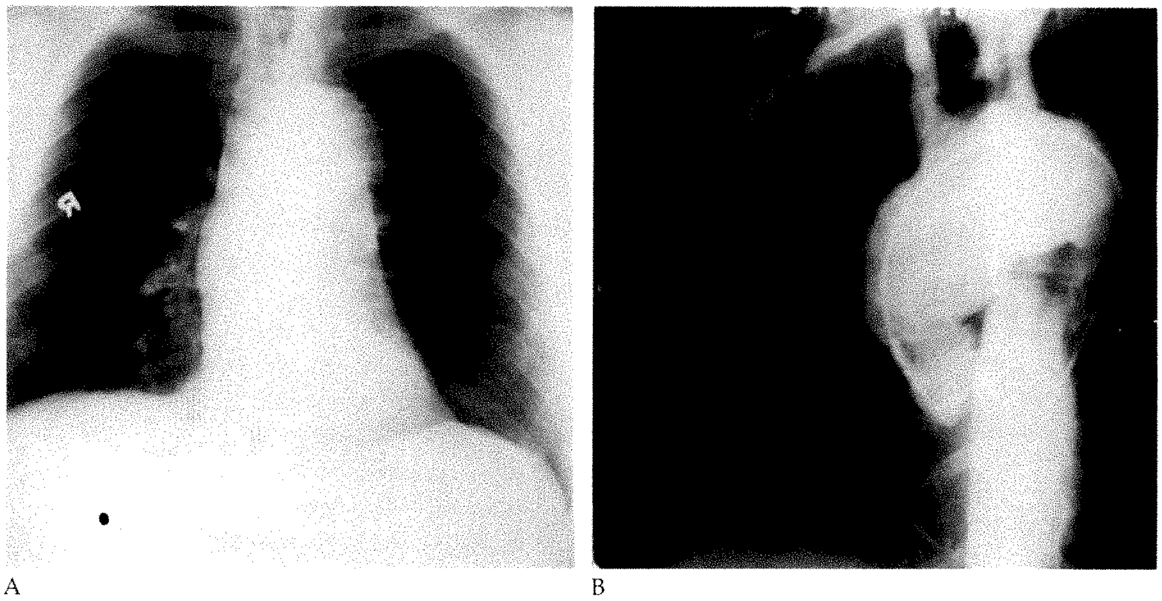


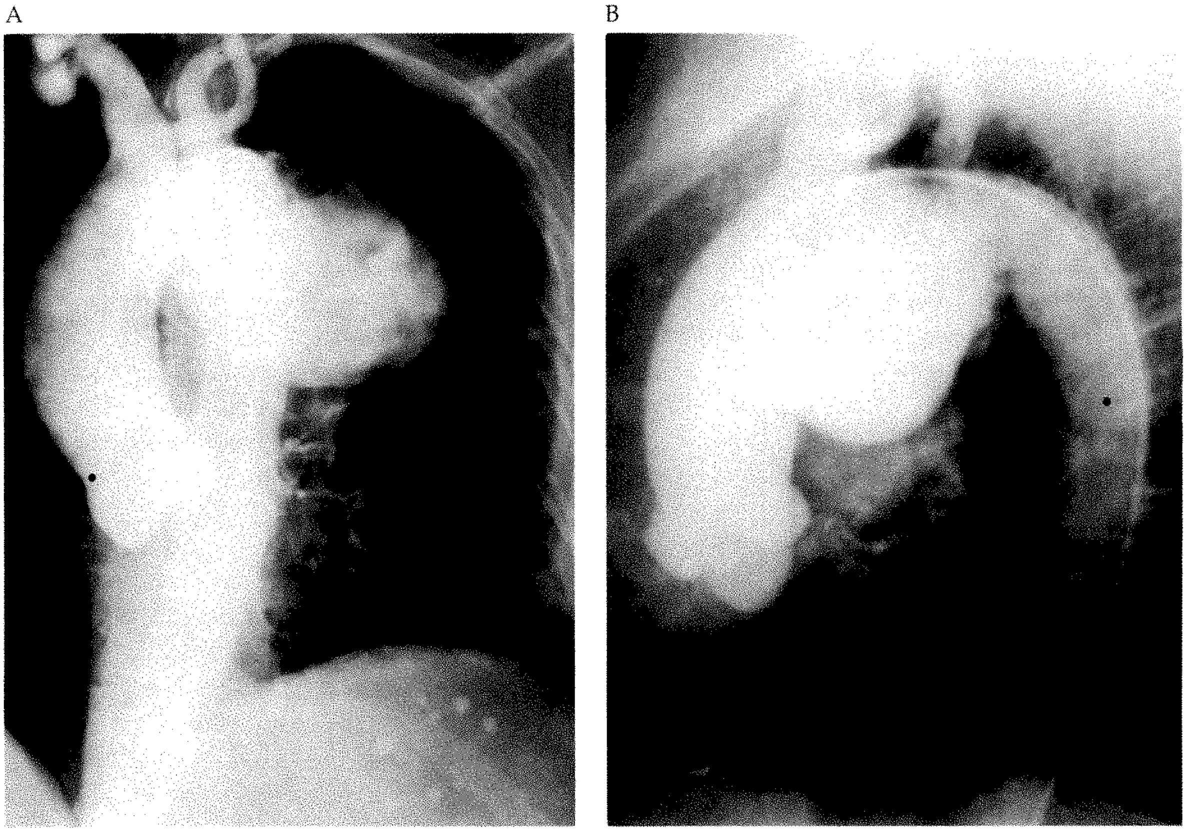
Fig 3. (Patient 3.) (A) Posteroanterior roentgenogram and (B) angiogram.

tinued. Postoperative convalescence was quite successful.

Patient 5

A 15-year-old boy was asymptomatic and had absent femoral pulses. Blood pressure in the right arm was 150/90 mm Hg and in the legs and

Fig 4. (Patient 4.) (A) Anteroposterior and (B) lateral aortograms.



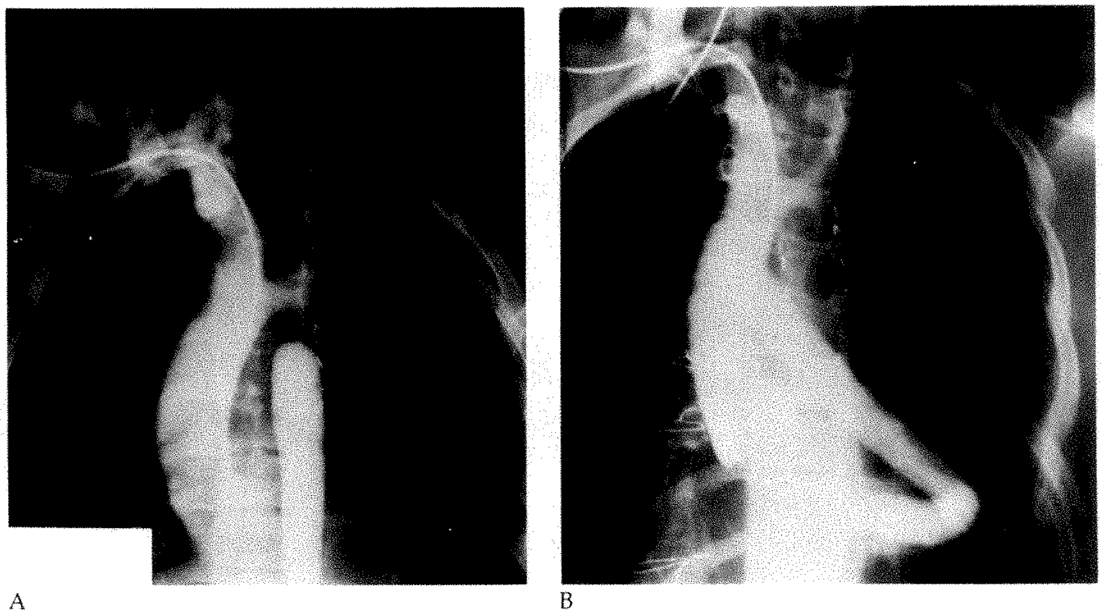


Fig 5. (Patient 5.) (A) Preoperative and (B) postoperative aortograms.

left arm, 90 mm Hg. Cardiac catheterization showed aortic obstruction thought to be located at the usual site of coarctation. At exploration, an interrupted aortic arch was found. Repeat angiography demonstrated this to be a type B interrupted aortic arch. The patient underwent bypass grafting from the ascending aorta to the descending aorta by means of a left posterolateral thoracotomy through the bed of the resected sixth rib and a median sternotomy. This permitted distal anastomosis to the descending aorta in a virgin field. The inferior pulmonary ligament was divided, and the graft was passed over the pulmonary artery to the ascending aorta where the proximal anastomosis was constructed, as shown in Figure 5. There was no pressure gradient between the descending aorta and the ascending aorta through the graft at the time of postoperative catheterization.

Technique

The patient is positioned in a 45-degree, right lateral decubitus position (Fig 6). A roll is placed in the right axilla, and another roll is used to support the patient's back. Two widths of 3-inch (7.62 cm) adhesive tape are used to fix the position of the hips so that the external iliac vessels can be isolated through an inguinal incision. An assistant elevates the left hand. The surgical preparation includes the neck, thorax, shoulder, abdomen, left groin, and left upper extremity to the level of the wrist. The left hand and forearm are then placed in a Lahey bag and covered with stockinette. A plastic drape is used to cover the entire field. The operative field lies to the right of the posterior midline from the middle of the thorax to the neck to facilitate the posterior limb of the thoracotomy.

Comment

A combined median sternotomy and posterolateral thoracotomy was utilized for five different reasons in the case reports cited. In Patient 1, the hypothermia and total circulatory arrest needed for repair of the aneurysm of a previously ligated ductus arteriosus necessitated catheterization of the right atrium and the ascending aorta. In Patient 2, proximal control for shunt placement was gained by the use of combined exposure in a patient with an extensive localized aortic dissection. In Patient 3, distal control and insertion of an arch graft for perfusion of the great vessels before and after cardiopulmonary bypass was achieved by use of this exposure. In Patient 4, use of this technique permitted exposure of the inferior surface of the aortic arch, which otherwise is extremely difficult to obtain. In Patient 5, this

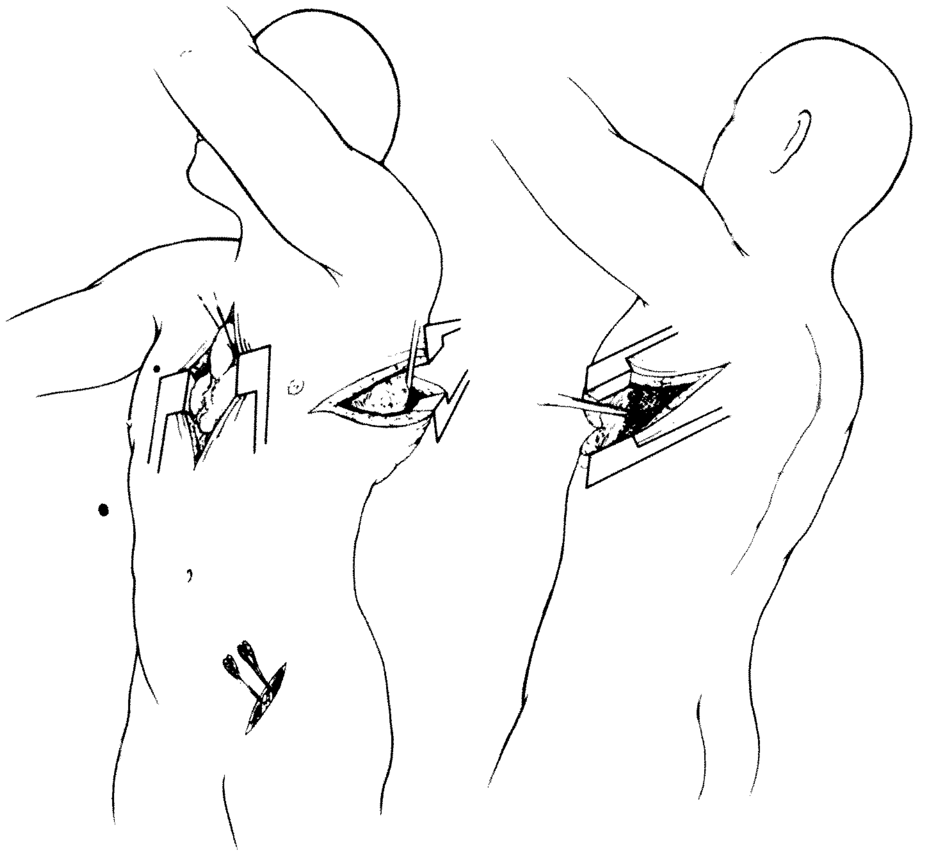


Fig 6. Position and approaches for combined median sternotomy and posterolateral thoracotomy.

approach permitted the exposure of both the descending aorta and the ascending aorta for bypass grafting of an interrupted aortic arch; both anastomoses could then be performed using virgin vessels.

This simultaneous approach was described by Doty and associates [2] in 1972 and used later by McGoon and colleagues [4] in the management of large bronchial collateral vessels during repairs of pulmonary stenosis or atresia. There are limited indications for such an extensive exposure. Other situations in which it might be useful include acute aortic dissections involving the arch vessels, traumatic aortic injury involving the arch, the arch vessels, or the region of the ligamentum arteriosum, as described by Castagna and Nelson [1] and Tector and colleagues [6], and secondary operation for coarctation of the aorta, as described by Edie [3], Siderys [5], and their associates.

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A Thumbtack Type of Needle Thermistor for Myocardial Protection

Tomio Abe, M.D., and Sakuzo Komatsu, M.D.

ABSTRACT **The most important and effective factor for myocardial protection during cardiac operation is to keep the myocardium at as low a temperature as possible. The ideal temperature is around 15°C. A thumbtack type of needle thermistor has been developed and used clinically and experimentally during myocardial protection. This type of needle thermistor has several definite advantages.**

Recent interest in the use of cold cardioplegia has made it the method of choice for protection of the myocardium during open-heart operation [3, 4]. We have investigated the effects of cold coronary perfusion with Ringer's lactate solution at 0 to 4°C, and combined it with modified Young's solution to keep the myocardial temperature below 15°C during two hours of aortic cross-clamping in left ventricular hypertrophied canine hearts. The results obtained from our experimental and clinical studies indicate that one of the most important and effective factors for myocardial protection is to maintain the myocardial temperature below 15°C (13° to 15°C) persistently, while the patient's temperature often is 30°C or higher [1, 2, 5]. Therefore, the key point for myocardial protection is that the hypertrophied or failed heart be cooled uniformly and continuously even at the endocardial layer during the operative procedure.

We have developed a thumbtack type of needle thermistor (manufactured by Fukuda Electrical Co., Sapporo, Japan) to measure the temperature of protected myocardium with cold cardioplegia (Fig 1).

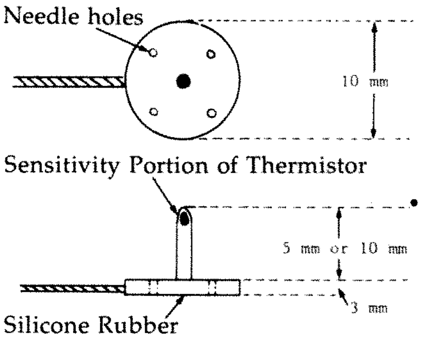

Fig 1. Thumbtack needle thermistor device.

Material and Method

The thumbtack is made of silicone rubber. The thumbtack thermistor is 1 mm in diameter at the tip. The two types of thermistor vary in length. One is 5 mm long and is for a child or the epicardium, and one is 10 mm long and is for an adult or the endocardium (Fig 2A). The thermistor can be affixed with 3-0 or 4-0 Tevdek sutures to the avascular portion of the right or left ventricle through four needle holes in the thumbtack (Fig 2B). The thermistor can be sterilized for clinical use.

Comment

Protection of the hypertrophied or failed myocardium has been investigated widely, and the use of cold cardioplegia and protective infusates has increased rapidly. Hypothermia is commonly employed to protect the myocardium during cardiac operations [6, 7]. Therefore, the need to measure myocardial temperature is very important during protection with cold cardioplegia, unless it is properly cooled and effectively preserved.

We sometimes have trouble putting the long straight or curved needle thermistor into myocardium. The needle can come out of the myocardium easily and cause damage to the surface of the myocardium. Also the needle thermistor occasionally gives the wrong temperature because it is pushed into the cavity of the ventricle.

Our thumbtack type of needle thermistor for myocardial protection has the following advantages:

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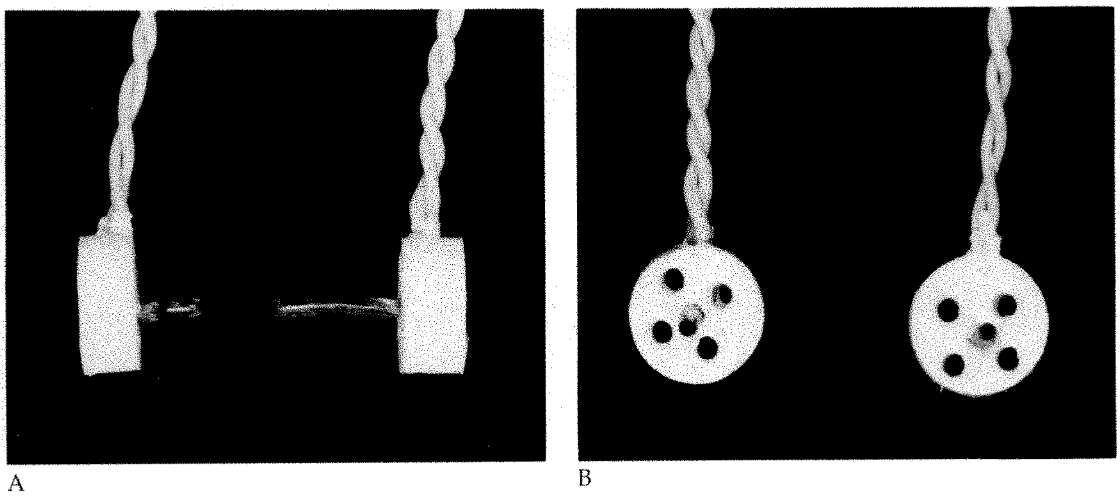

Fig 2. (A) The thumbtack needle thermistor for myocardial protection during cardiac operation: left, 5 mm length; right, 10 mm length. (B) The four needle holes allow the thermistor to be fixed on the myocardium.

1. Continuous measurement of temperature at the same level of the myocardium is possible during the cardiac operation.
2. Only minimum damage occurs to the myocardium even if the heart is returned to normal beat and is elevated to evacuate air from its apex.
3. The correct needle for the size of the heart can be selected, and the two types of needle can be used simultaneously to measure the temperature of the epicardium or endocardium in an experimental study.
4. The thumbtack needle thermistor does not disturb the operative procedure and field.
5. The error of temperature recording with this device is ±0.1°C between 5° and 42°C.

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Myocardial Protection: A Safe Cardioplegic Catheter

Peter A. Philips, M.D., and Herbert Dan Adams, M.D.

ABSTRACT **The administration of cold cardioplegic solution has contributed to the "safe" time allowable for performance of intricate cardiac procedures under ischemic arrest. A catheter has been designed that delivers a large bolus of solution quickly, ensures rapid arrest of cardiac function, and allows continuous perfusion during the procedure. It permits the safe escape of air on reestablishment of cardiac function. The catheter can be inserted and removed through a small aortotomy, thereby preventing undue trauma to a sclerotic or thickened aorta.**

The use of cold potassium cardioplegia during cardiopulmonary bypass has allowed longer, safer periods of ischemia for complicated cardiac surgical procedures. There are differences in solution contents and various methods for application, but the ready delivery of cold potassium in adequate aliquots is the important and essential factor for prompt cessation of myocardial contractility. A catheter has been designed that (1) can be inserted and removed with minimal trauma to the aorta, (2) allows for instillation of cardioplegic solution quickly and in large volume, and (3) provides an escape for air from the ascending aorta and left ventricle on reestablishment of cardiac action following release of the aortic cross-clamp (Fig 1).

A No. 11 knife blade is used to make a small opening in the ascending aorta. The 10F beveled end of the catheter can be slipped easily through the opening, and the 1.5 cc balloon is filled with saline solution (Fig 2). Then the catheter is pulled back gently until the balloon occludes the entrance site. A pursestring stitch can be placed about the catheter to hold the selected position and to close the tiny aortotomy on removal of the catheter. The balloon prevents the catheter from slipping out of the aorta once it is positioned.

The cardioplegic balloon-tipped catheter can be used to selectively perfuse the coronary arteries with cardioplegic solution during aortic valve replacement (Fig 3). The balloon is quickly deflated by turning the stopcock, and the tip is placed in the appropriate coronary ostium.

Our method of cardioplegic instillation requires a rapid delivery of 250 to 300 ml of solution under pressure followed by continuous drip throughout the operation. We believe that continuous perfusion maintains a constant cold temperature across the myocardium, provides continuous washout of cellular metabolic products, and allows a clear field across the coronary arteriotomy for fine suturing. Following com-

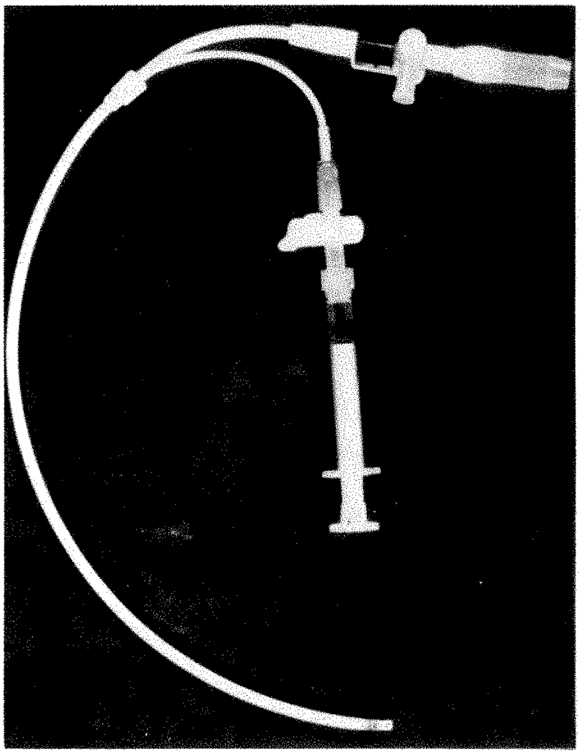

Fig 1. The cardioplegic catheter, which consists of a small 1.5 cc balloon located just proximal to the beveled tip of the catheter, two stopcocks for placement of saline solution in the balloon, and the attachment for the cardioplegic solution and evacuation of air.

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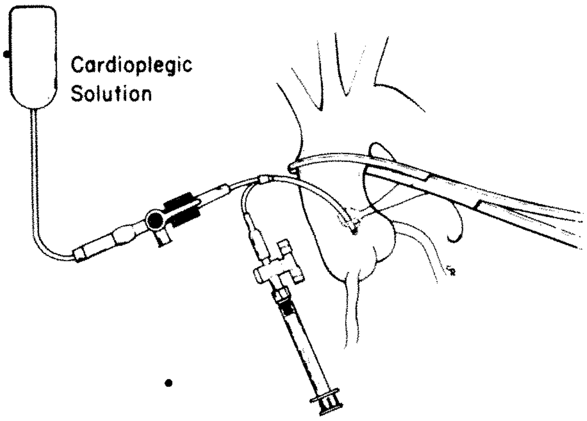

Fig 2. The catheter is placed through the opening, the balloon is inflated, and solution is injected.

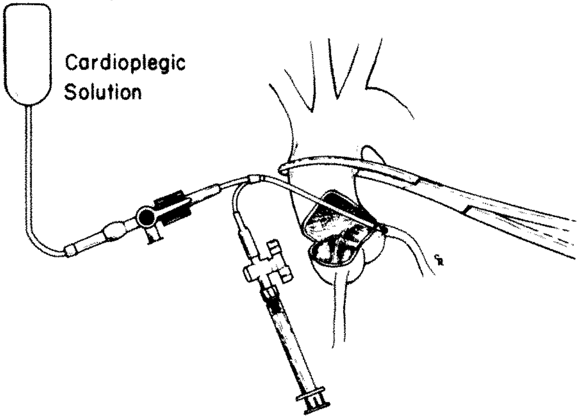

Fig 3. The balloon-tipped cardioplegic catheter in the coronary artery during aortic valve procedure. The catheter can be moved to the right ostium for cardioplegic perfusion. The balloon is deflated during direct perfusion.

pletion of all anastomoses and prior to removal of the aortic cross-clamp, the proximal end of the catheter is detached from the cardioplegic line and connected to the cardiopulmonary bypass unit. Suction is begun as the cross-clamp is removed. This procedure ensures the successful evacuation of air from the proximal aorta and left ventricle.

This catheter was designed for several specific purposes. It ensures that a large aliquot of cardioplegic solution can be delivered quickly. It allows a steady, constant amount of solution for continued coronary perfusion. It permits safe insertion and removal with minimal aortic trauma. It remains in place during the procedure out of the surgeon's way. It ensures safe evacuation of air from the aorta and left ventricle.

The cardioplegic catheter has been utilized in 10 patients with no untoward effects. It can deliver 350 to 400 ml of solution per minute under pressure and withdraw 650 to 750 ml of a blood-air mixture per minute during reperfusion. Since using this unit, we have not experienced aortic tearing requiring multiple aortic sutures and have had no difficulties with sclerotic or thickened aortas. We think the cardioplegic catheter constitutes an improved and safer method of providing myocardial protection.

Addendum

An additional 12 patients have been treated utilizing this cardioplegic catheter, with results similar to those just reported. A question was raised as to the possibility of air being trapped between the balloon and the aorta, and we directed our attention to this matter. We noted that upon release of the balloon prior to its removal from the ascending aorta, we could not demonstrate the presence of trapped air. We attempted to do this by placing a needle directly alongside the small arteriotomy and by leaving the arteriotomy open upon removal of the balloon. No air was noted. Now, as an extra safety precaution, upon collapse of the balloon, we maintain suction on the cardioplegic catheter as it is withdrawn through the arteriotomy. We have experienced no problems that could be construed to be caused by air.

Delayed LV Rupture

To the Editor:

The article by Dr. Nuñez and co-workers, entitled "Delayed Rupture of the Left Ventricle after Mitral Valve Replacement with Bioprosthesis" (Ann Thorac Surg 27:465, 1979) was very timely and emphasized to readers the existence of etiological factors related to the morphology of this particular prosthetic device that are responsible for this complication.

Rupture of the left ventricle following mitral valve replacement has been described with a variety of prosthetic devices. This clearly indicates that the complication has variable iatrogenesis [1, 2]. In quoting from one of our previous publications [2], the authors drew an incorrect conclusion from our statement that there was no relationship between the type of prosthesis used and the incidence of this complication. We were referring to the cases under review in which the postulated etiological factors were clearly different and in which the complication occurred indifferently in the presence of a high- or low-profile prosthesis. We agree with Dr. Nuñez' implications regarding the mechanics of left ventricular rupture after mitral valve replacement using the described bioprosthesis, but we also believe that other factors, related either to the device or its mechanics of insertion, can be responsible for such catastrophic complications.

One of the most critical points is the technique of lowering the bioprosthesis into position. Because an anterior approach (median sternotomy) is used in most instances, there is a tendency to lower the prosthesis into position at an angle almost perpendicular to the long axis of the heart. Inadvertently, the surgeon can force the struts of the prosthesis against the posterior wall of the left ventricle, causing trauma in this area. Also, during this part of the procedure, there is a tendency to maintain some tension in the sutures to avoid their being looped around the struts of the bioprosthesis. This creates a fixed point—the posterior wall of the left ventricle—against which the valve is pushed during its descent into position. The possibility of rupture at this particular point is greatly enhanced by the softness of the myocardium when cardioplegic solution has been used. We believe that this situation can be avoided if the valve is slid into position following a parallel orientation with the long axis of the heart in such a way that the struts are not forced against the posterior ventricular wall but are oriented toward the apex of the left ventricle. We encountered a situation in which the strut of the porcine heterograft was completely embedded in the posterior wall of the left ventricle without having caused a perforation in this area. This event was recognized at operation, and the problem was repaired successfully.

It should also be remembered that in using this bioprosthesis, surgeons have a tendency to select the largest prosthesis possible in order to avoid a transvalvular gradient. In so doing, they may select a larger valve than is advisable. Also, in patients with a small left ventricular cavity, such a prosthesis could be responsible for undue pressure in the posterior wall of the left ventricle and cause final rupture.

Once again, we congratulate the authors. We share their surprise that with the extensive use of bioprostheses at present, rupture of the left ventricle after mitral valve replacement is not reported more often.

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Reply

To the Editor:

We thank Dr. Zacharias for his interesting letter regarding our article and have a few comments to make in return. The purpose of our article was to emphasize the danger of perforation of the posterior ventricular wall during insertion of a mitral bioprosthesis. We believe there are multiple factors that contribute to this very lethal complication. Some factors are common to mitral valve replacement and are not related to the type of mitral prosthesis used. However, bioprostheses specifically are dangerous because of their posterior strut.

After the prosthesis is inserted, the struts do *not* face the posterior ventricular wall but the outflow tract of the left ventricle. This is seen by looking through the aortic orifice at double-valve replacement or from the apex of the left ventricle at postmortem examination. It seems clear to us that perforation or posterior strut impingement on the posterior wall must happen either when the valve is lowered into position, as Dr. Zacharias points out, or when air is evacuated from the left ventricle by lifting the heart out of the pericardium and contact is produced between the left ventricular wall and the posterior strut.

Surgeons using a continuous suture technique may not have this complication because the lowering of the valve is done in a more favorable way. We have had three perforations by the posterior strut in 308 mitral valve replacements with a bioprosthesis. All occurred in women undergoing isolated mitral valve replacement in whom the valve was inserted with interrupted sutures. We had no perforation in 210 procedures in which a continuous suture technique was used.

In conclusion, we hope that if surgeons are very conscious of the posterior strut during lowering of the bioprosthesis as well as during evacuation of air from the left ventricle, especially in women requiring isolated valve replacement, this almost lethal complication will become less frequent.

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Axillofemoral Graft

To the Editor:

The ingenious "How to Do It" paper by Dr. Tangpraphaphorn and his colleagues, entitled "Axillofemoral Bypass: Intrapleural Method" (Ann Thorac Surg 27:80, 1979) can be viewed as a suggestion for an alternative route to a procedure which itself is an extraanatomical alternative route procedure. Extraanatomical routes have been adopted by vascular surgeons to avoid thoracotomy or laparotomy in poor-risk patients and to bypass areas of infection in prostheses or anastomoses. If an alternative route graft, such as an axillofemoral bypass is used often enough, the need to bypass part of it will arise sooner or later.

The intrapleural method described by Dr. Tangpraphaphorn and co-workers suggests an ideal solution to a problem in one of our patients with a chronic infection of part of an axillofemoral graft just behind the breast. After the patient experienced early postoperative graft occlusion, a skin incision in the area had been reopened and a Fogarty catheter passed to reestablish flow. The incision became infected with *Staphylococcus aureus,* and eventually the graft had to be removed. Rerouting a fresh graft by the intrapleural method could well have saved that particular graft.

The intrapleural route could also be an alternative to the regular subcutaneous route in women with mastectomy scars whether or not they underwent radiation therapy. It would avoid the hazard of tumor recurrence over a graft.

It must be remembered, however, that the validity of the authors' reason for preferring this route, namely, that it will decrease late occlusion rates, remains to be proved, as they stated.

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Sheba Medical Center
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REVIEW OF RECENT BOOKS

A Manual of Thoracic Surgery

By Arndt Von Hippel, M.D.,
Springfield, IL, Charles C Thomas, 1978
247 pp, illustrated, $9.75 paperback, $16.00 hard cover

Reviewed by Max J. Trummer, M.D.

The dust jacket states: "This is a basic, practical up-to-date manual for the evaluation and treatment of patients with thoracic surgical problems. The text employs, as a focal point or unifying concept, the manner in which physiology and surgery relate to closed chest drainage. An easy narrative style and logical presentation of material make this book exceptionally coherent and effective."

The book indeed is very pragmatic. The author's views are based on keen observation, an extensive experience, and an intimate knowledge of the current literature, and they are presented clearly. The style is anecdotal, and no subject is treated in-depth except the concept of closed chest drainage. The reader is not overwhelmed with statistical analyses of various groups of patients. No references are cited, which makes for easier reading but means there are no signposts for additional study.

Particularly intriguing is the author's advocacy of outpatient treatment for spontaneous pneumothorax (or prolonged postoperative air leaks). The patient pursues virtually normal activity with a chest tube, connected to a portable underwater-seal drainage system, in place. I see no reason why this should not succeed. However, I suspect that Dr. Von Hippel's patients in Anchorage are more self-reliant than the litigious-minded welfare patients so frequently seen in southern California.

The outstanding value of the book is the thorough discussion of both the proper management of the chest tube and the information provided by the chest tube regarding the status of the lung and pleural space. In the words of the author, the chest tube always "tells the truth"; however, the art of understanding the message given by the chest tube is largely neglected or ignored by the cult of modern technology. I am not ready to limit the use of suction to only those patients with a large air leak, but otherwise I am in full agreement with the author. He is to be congratulated for presenting a wealth of valuable details for the successful conduct of chest drainage. The book additionally includes a broad range of thoracic surgical topics related to the diaphragm, chest wall, pleura, mediastinum, lung, "the blood pump," and the pericardium.

I highly recommend this book to all current thoracic surgery housestaff, recent graduates, and nurses responsible for the care of patients with chest tubes.

San Diego, CA

The Practice of Coronary Artery Bypass Surgery

By Donald W. Miller, Jr., M.D.
New York, Plenum Publishing Corporation, 1977
237 pp, illustrated, $19.50

Reviewed by Quentin R. Stiles, M.D.

This book is written by a cardiac surgeon but it is not a presentation of the facts and figures from his personal operative experience. Instead it represents (1) a summary of a review of the literature, both medical and surgical, (2) a report of a questionnaire survey of 400 cardiac surgeons in the United States, and (3) the author's own interpretation of or feelings about various aspects of coronary artery disease and operations. He was very clear in identifying his sources of information or to remark when certain statements were not specifically supported by scientific documentation.

The book was published in 1977, and represents the thinking and knowledge in the "second generation" of coronary artery operations when the operative mortality had become low and the importance of myocardial protection was appreciated. The author frequently pointed out when some reported data were taken from the "early years" and might be expected to be different from current figures.

The review of the literature is extensive but is reported in very concise, "essentials only" style. It is material of which both cardiac surgeons and cardiologists should be aware. Physicians referring patients for coronary artery angiography or operation also should have knowledge of this information. For example, chapter 2, entitled "The Clinical Course of Patients with Coronary Artery Disease," reviews the clinical states presented by coronary artery disease and the natural course of the various coronary events such as angina, infarction, and sudden death. Chapter 3 discusses the benefits of coronary artery surgery. The case for producing improvement in ventricular function, which might result in prolongation of life, is stated fairly without excessive claims of benefit. Chapter 6 covers the factors influencing selection of patients for operation. The author does not present a detailed outline that definitely indicates whether a specific patient should or should not undergo coronary surgery. Instead, he discusses various factors such as angiographic anatomy, ventriculography, stress test evaluation of function, and clinical course to guide the reader's thinking. He does a good job of making it obvious why the decision for or against operation is often difficult because of its complexity and because some of the data and knowledge necessary for a rational decision are still lacking.

The report of the questionnaire sent to 400 cardiac surgeons is interesting in that it summarizes points of technique in which the surgeons tend to agree or differ.

The last chapter, entitled "The Economics of Bypass Surgery," is an attempt to wrestle with the problems of the high cost to society of both the disease and the treatment. The difficulties of a cost-effective analysis of the operation are presented clearly. The author also points out the rather profound effects this type of operation has had on other fields of medicine, such as exercise cardiology, laboratory detection of myocardial damage, and cardiac epidemiology.

The book is a gem, and I recommend it to all who are interested in any aspects of coronary artery disease. Because of its extensive review of the literature, it is a handy first place to look when one is preparing a report regarding coronary artery disease or surgery and needs to obtain proper background information.

Los Angeles, CA

Cardiology Update: Reviews for Physicians

Edited by Elliot Rapaport, M.D.
New York, Elsevier North Holland, 1979
364 pp, illustrated, $24.95

Reviewed by Robert B. Karp, M.D.

Cardiology Update 1979 is the first volume of a series of annual publications intended for generalists and specialists as a review of specific cardiological and cardiac surgical areas. In the first two chapters, Popp and associates present a nice "primer" on echocardiography. They use particularly clear illustrations of frequently encountered conditions and discuss both M-mode and two-dimensional echocardiography in a lucid fashion. Four excellent chapters deal with the use of radionuclides for cardiac diagnosis. The editors chose acknowledged experts to write about gated cardiac pool imaging, radionuclide exercise angiography, myocardial imaging, and evaluation of cardiac output in pulmonary disease. A further chapter offers a nice twist by taking a "vertical cut" of the chapters preceding and offering an insight into the modalities for obtaining noninvasive assessment of left ventricular performance.

Newer aspects of electrophysiology are covered in the next three chapters, which are informative by and large. However, the reader might wonder whether the surgical treatment of supraventricular reentrant tachycardia could not have been explored further.

In a discussion of treatment of unstable angina, Kouchoukos gives a reasoned exposition of the combined initial medical and delayed surgical approach used at the University of Alabama. The next chapter, on xenografts, is excellent as far as it goes. However, more tabular and actuarial data (alluded to but not included) pertaining to Ries's experience with the durability of, hydraulic performance of, and thromboembolic events with xenografts could have been provided.

The final three chapters contain important information for quick reference on intraaortic balloon assist, workup of hypertension, and newer modalities in the medical treatment of hypertension.

This volume is an excellent reference for generalists and housestaff and for individuals needing ready access to information not directly in their own field of endeavor. With few exceptions, the book is free from editorial and typographical errors and is arranged in a pleasing format. It is to be hoped that the subsequent annuals will be as good.

Birmingham, AL

SEVENTEENTH ANNUAL MEETING OF THE SOCIETY OF THORACIC SURGEONS

Los Angeles, CA
January 26–28, 1981

The Seventeenth Annual Meeting of The Society of Thoracic Surgeons will be held at the Los Angeles Bonaventure Hotel, January 26–28, 1981.

Application for Membership
(Deadline: September 1, 1980)

Requests for application forms for membership in The Society of Thoracic Surgeons should be addressed to Quentin R. Stiles, M.D., Chairman, Membership Committee, The Society of Thoracic Surgeons, 111 E Wacker Dr, Chicago, IL 60601.

The completed application forms and supporting letters must be in the hands of the Membership Committee by **September 1, 1980,** for the applicant to be considered for election at the meeting next January.

Call for Abstracts—1981 Meeting
(Deadline: August 31, 1980)

Abstracts for papers to be presented at the 1981 annual meeting are now being accepted. The deadline for receipt of abstracts is **August 31, 1980.** An original and 9 copies should be submitted, using the official Society abstract form (on verso of this page), to W. Spencer Payne, M.D., Chairman, Program Committee (Abstracts), The Society of Thoracic Surgeons, 111 E Wacker Dr, Chicago, IL 60601. Additional forms are available upon request from the Society. Abstracts must summarize an original contribution not presented or submitted elsewhere. Abstracts received after the deadline will not be considered. It is requested that the covering letter indicate the author who is to receive notice of acceptance or rejection and the author who will present the paper.

Essayists are reminded that according to the bylaws of the Society, all papers accepted for presentation: (1) must be submitted in duplicate to the Secretary at the time of presentation or to the Editor of *The Annals of Thoracic Surgery* prior to presentation; and (2) become the property of the Society if they are accepted for publication, in which case they may not be published other than in *The Annals of Thoracic Surgery.*

It is well recognized that abstracts frequently belie their content by virtue of poor organization, and as a result valuable contributions to the Scientific Sessions may be unrecognized. It is important that methods and results be clearly defined in the abstract; therefore, general statements such as "results will be presented" are not acceptable. When a procedure or method is stated to have "advantages," those advantages should be defined. Abstracts that simply summarize results without defining objectives and methods are equally undesirable.

Speakers for accepted papers are limited to 10 minutes.

Instructions for Abstracts

The official abstract form printed on verso of this page and available from the Society, or photocopies thereof, must be used. Authors must categorize the principal subject of their abstract using the code at the top of the form, and insert the proper code in the box provided in the upper left corner of the form.

1. Full names of authors must appear on the abstract.
2. Institution or address is to be given, but omit titles, degrees, and appointments.
3. Abstracts must be limited to 250 words and must be typed double-spaced.
4. When percentages are used, the absolute numbers of derivation must be stated.
5. The body of the abstract should include:
   a. A brief statement of the purpose of the study being presented, with reference to the current state of research in the field.
   b. The methods of study or experimental approach, clearly but briefly defined.
   c. A summary of the results and/or conclusions of the study, including sufficient details to support those conclusions.
   d. A statement concerning the significance of the work and its possible implications for future research; "results will be presented" is unacceptable.
6. The form must be signed by the senior author attesting that the material will not be published elsewhere if accepted for publication in *The Annals of Thoracic Surgery.*

In discussion of papers, the Society encourages a healthy spirit of constructive critical review and rebuttal by comments pertinent to the content of the paper being presented. Presentation of discussion in the form of "secondary papers" will not be welcomed.

Call for Surgical Films
(Deadline: August 31, 1980)

The popular surgical movie program will again be presented at the Los Angeles meeting. The Program Committee hereby solicits the submission of surgical films, which may portray a surgical procedure or simply a technical maneuver that the surgeon thinks will be of interest to the Society. The film may not exceed 10 minutes in length. Sound movies are acceptable but not necessary, and live narration by the principal surgeon is a requirement for participation in the movie night program. The movies may be on Super-8 or 16-mm film. The deadline for submission of films is **August 31, 1980.** Films also should be sent to W. Spencer Payne, M.D., Chairman, Program Committee, at the Society office, 111 E Wacker Dr, Chicago, IL 60601.

W. Gerald Rainer, M.D.
Secretary

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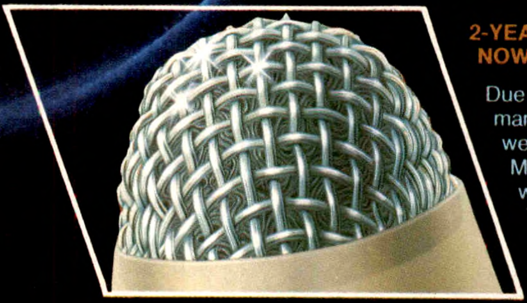

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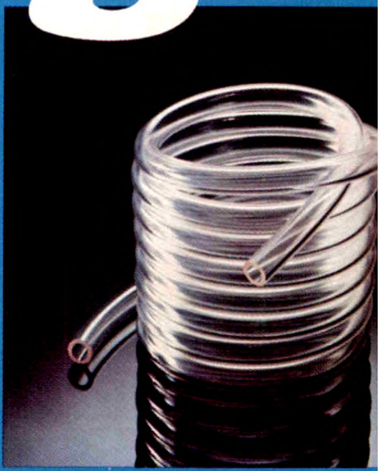

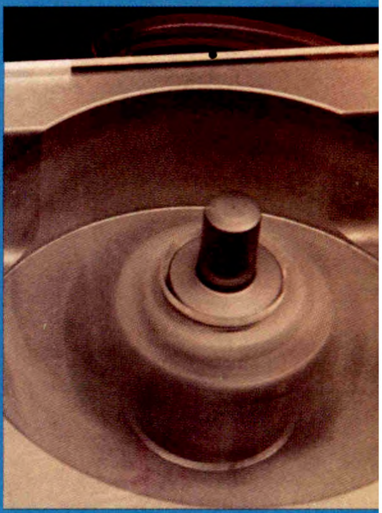

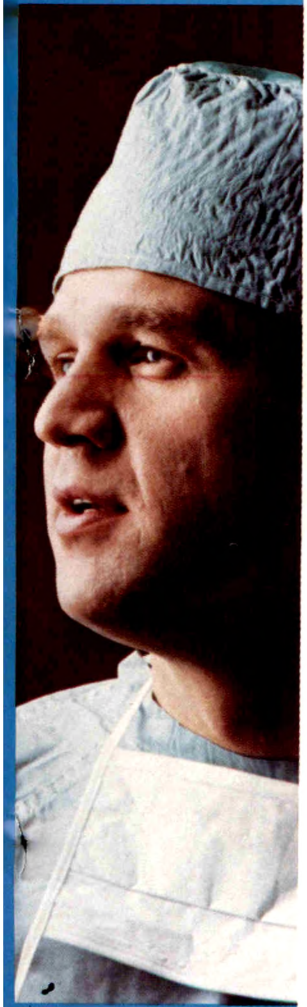

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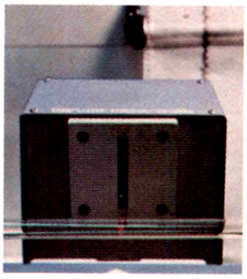

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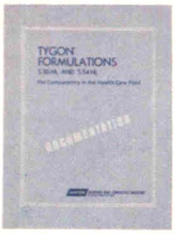

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Please submit full information with each ad, including name, address, and telephone number of contact person. If anonymity is desired when advertising a position wanted or available, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in *The Annals* Editorial Office and will be conveyed to the advertiser shortly after receipt.

Ads must be submitted no later than eight weeks prior to the publication month of the desired issue. Send ad and *nonrefundable* check (in the amount of $25 for every 50 words times the number of issues the ad is to run), payable to *The Annals of Thoracic Surgery,* to: Herbert Sloan, M.D., Editor, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

SITUATIONS WANTED

Thoracic and cardiovascular surgeon, 37, ABTS, ABS certified. Well trained in all facets of thoracic, cardiac, and peripheral vascular surgery, including angio-access. Seeking affiliation leading to partnership with a cardiothoracic group. Available immediately.

Please respond to W-225, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiothoracic surgeon, 39, ABS, ABTS certified, presently in private practice for two years, desires to relocate. Experienced in all facets of adult cardiac surgery.

Please respond to W-226, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiothoracic surgeon, 40s, presently in charge of cardiac service at University center, wishes to join well-established, hospital-based cardiac group. No geographical preference.

Please respond to W-228, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Thoracic, cardiovascular surgeon, certified, 48, university trained. Cardiovascular residency, 1971. Very experienced thoracic, vascular, angiograms, dialysis access, pacemakers. Moderate open-heart experience. Could develop rapidly in active practice because of previous experience. Understands physiology. Will consider any location, solo, group, with or without open heart.

Please respond to W-229, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Seasoned **cardiac and thoracic surgeon** currently at mid-career in full-time academic practice seeks situation in private sector. Opportunity to initiate new program in cardiac surgery preferred. Area and details flexible. ABS, ABTS certified. FACS, FACC, STS, AATS.

Please respond to W-230, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon, 35, well trained at major university center, seeks faculty position or association with private group. No geographic preference. Available immediately.

Please respond to W-231, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon wishes to relocate. ABS, ABTS certified, university trained; publications, three years' experience in adult cardiac, thoracic and vascular surgery in private practice. No geographic preference.

Please respond to W-233, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

SITUATIONS AVAILABLE

Associate sought in private practice limited to thoracic, peripheral vascular, and pacemaker surgery. Metropolitan area on East Coast. ABTS certified or candidate.

Please respond to Marvin L. Kolkin, M.D., P.A., 18111 Prince Philip Dr, Olney, MD 20832; tel: (301) 924-4880.

Fellowship in thoracic and cardiovascular surgery available 1980.

Contact Drs Urschel and Razzuk, Baylor University Medical Center, 3500 Gaston Ave, Dallas, TX 75246; tel: (214) 824-2503.

Fellowship in thoracic and cardiovascular surgery available in active program beginning July 1, 1980.

Please respond to A-173, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Thoracic vascular surgeon needed for group of internists-cardiologists. Expertise in pacemakers; some general, no cardiac surgery. Must be ABS, ABTS eligible or certified. Located on Florida's Gulf Coast.

Please respond to A-179, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiothoracic and vascular surgeon wanted to join two-man group in eastern Pennsylvania. Must be ABTS certified or eligible. Would prefer someone genuinely interested in living in this area.

Please respond to A-186, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiac surgeon with experience in vascular and pulmonary-esophageal surgery wanted. Must be ABTS certified or eligible. Practice located near West Coast in rapidly growing city. Recent graduate preferred; attractive terms with early partnership. Excellent opportunity for young enthusiastic surgeon.

Please respond to A-188, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Full-time position available in growing southeastern **university cardiac surgery program.** Clinical ability, teaching and research interests required.

Please respond to A-189, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

General thoracic surgeon wanted, certified or Board eligible, to join three-man surgical group based in one hospital in New York City.

Please send curriculum vitae to A-191, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Thoracic and cardiovascular surgeon wanted. Ninety-member multispecialty group adjacent to modern, accredited 480-bed hospital with a cardiovascular intensive care unit seeks Board-eligible or Board-certified specialist to join three thoracic and cardiovascular associates. Located in university metropolitan area of 105,000 in upper Midwest, 35 minutes from superb lake region. Associated with four-year medical school. Salary negotiable. All specialties represented. Will pay expenses for physician and spouse for interview.

Please respond to A-194, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon wanted for growing practice on West Coast. Applicant must be ABTS eligible or certified.

Send curriculum vitae to A-195, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Thoracic and vascular surgeon wanted to join private practice in mid-Atlantic coastal community. ABTS certified or candidate.

Please respond to E. W. Winfrey, III, M.D., 719 J. Clyde Morris Blvd, Newport News, VA 23601.

Cardiovascular and thoracic surgeon wanted, to begin this summer. Growing practice in greater Chicago metropolitan area.

Please send curriculum vitae to Raj B. Lal, M.D., 7607 W North Ave, River Forest, IL 60305; tel: (312) 366-7577.

Cardiovascular thoracic surgery fellowships (2) start July 1, 1980. Active open-heart program; clinical cardiovascular research opportunity; at least three years of surgical training required. Stipend plus attractive fringe benefits. Rental housing available; annual conference attendance provided.

Contact Dr. Adrian Kantrowitz, Chief, Cardiovascular Surgery, Sinai Hospital of Detroit, 6767 W Outer Dr, Detroit, MI 48235; tel: (313) 493-5775.

Fellowship in cardiovascular surgery available. Applicants should have completed general surgical training. Excellent opportunity for clinical and research experience in cardiovascular surgery offered. University cardiovascular program.

Please respond to A-199, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon wanted. Position immediately available with three-man practice in state in Sun Belt. ABTS certified or eligible; university training preferable.

Please respond with curriculum vitae to A-202, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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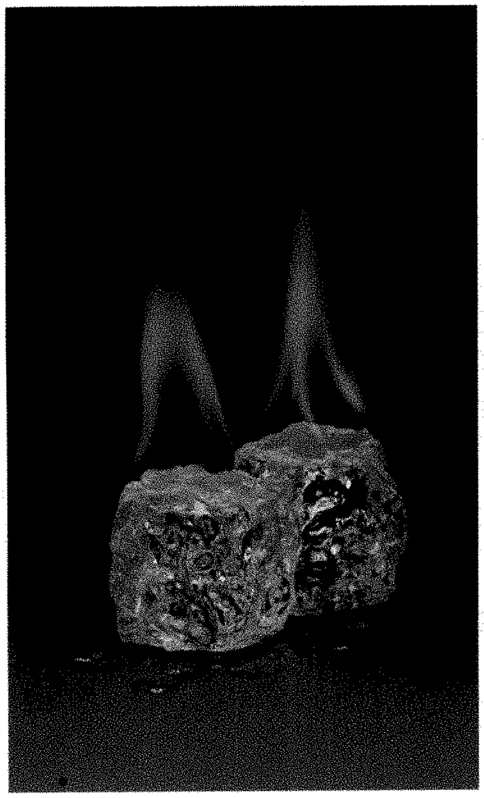

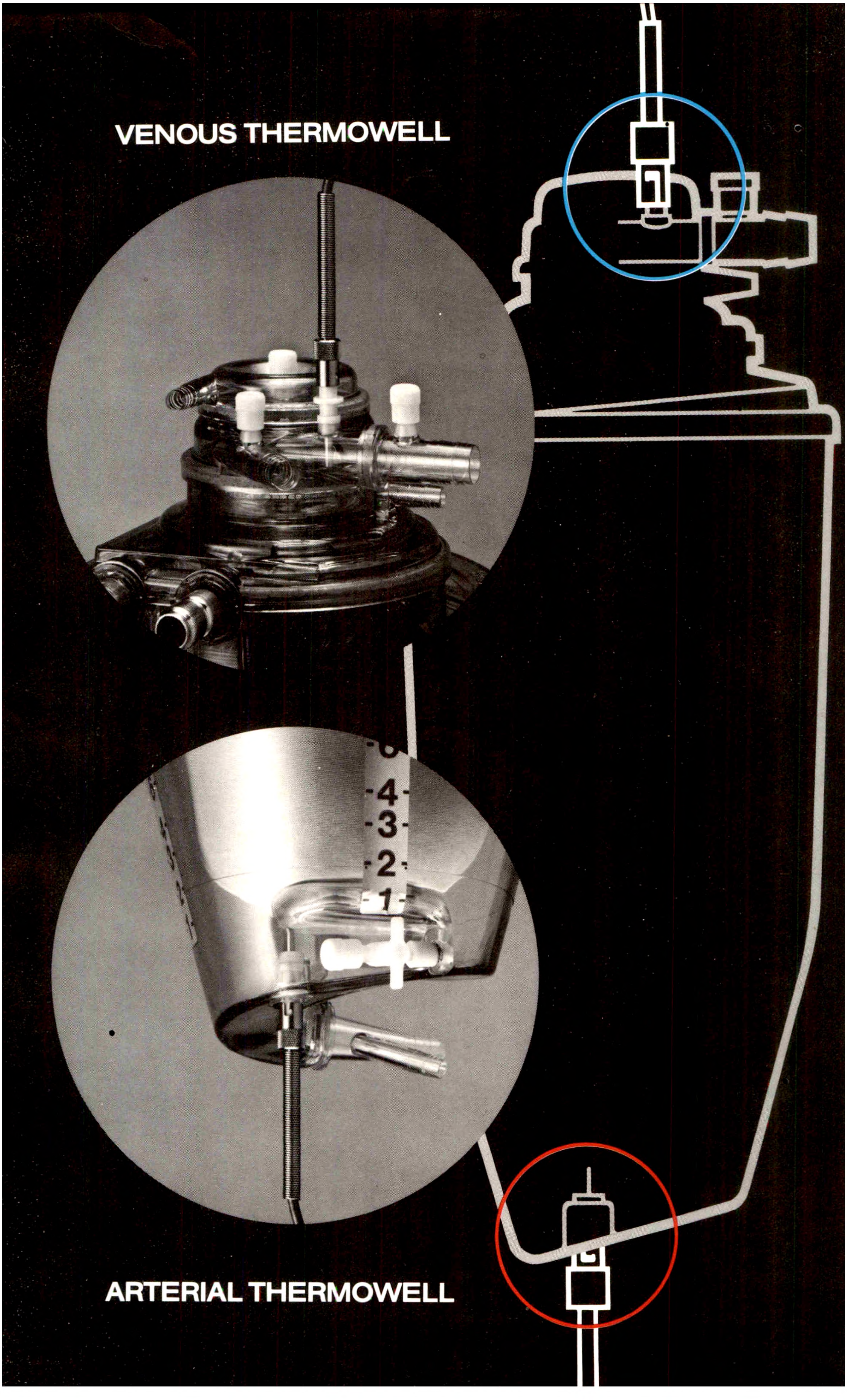
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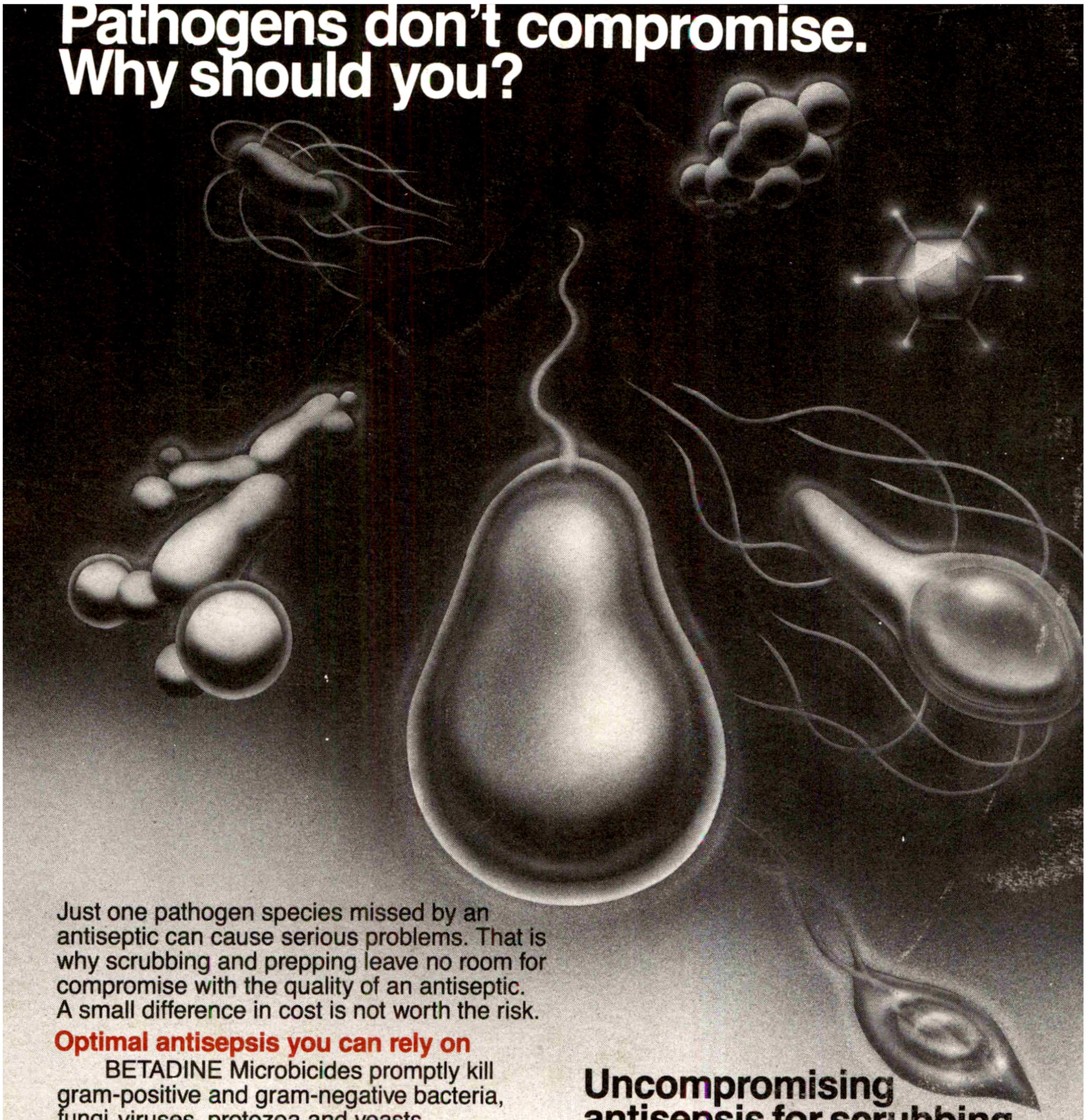

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THE ANNALS OF THORACIC SURGERY

Volume 30 Number 2 August 1980

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Call for Abstracts, The Society of Thoracic Surgeons, page A-21 (Deadline, August 31, 1980)

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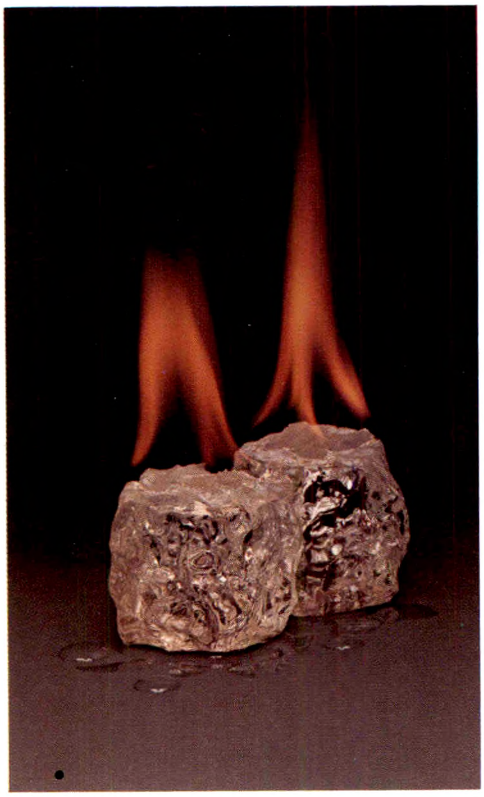

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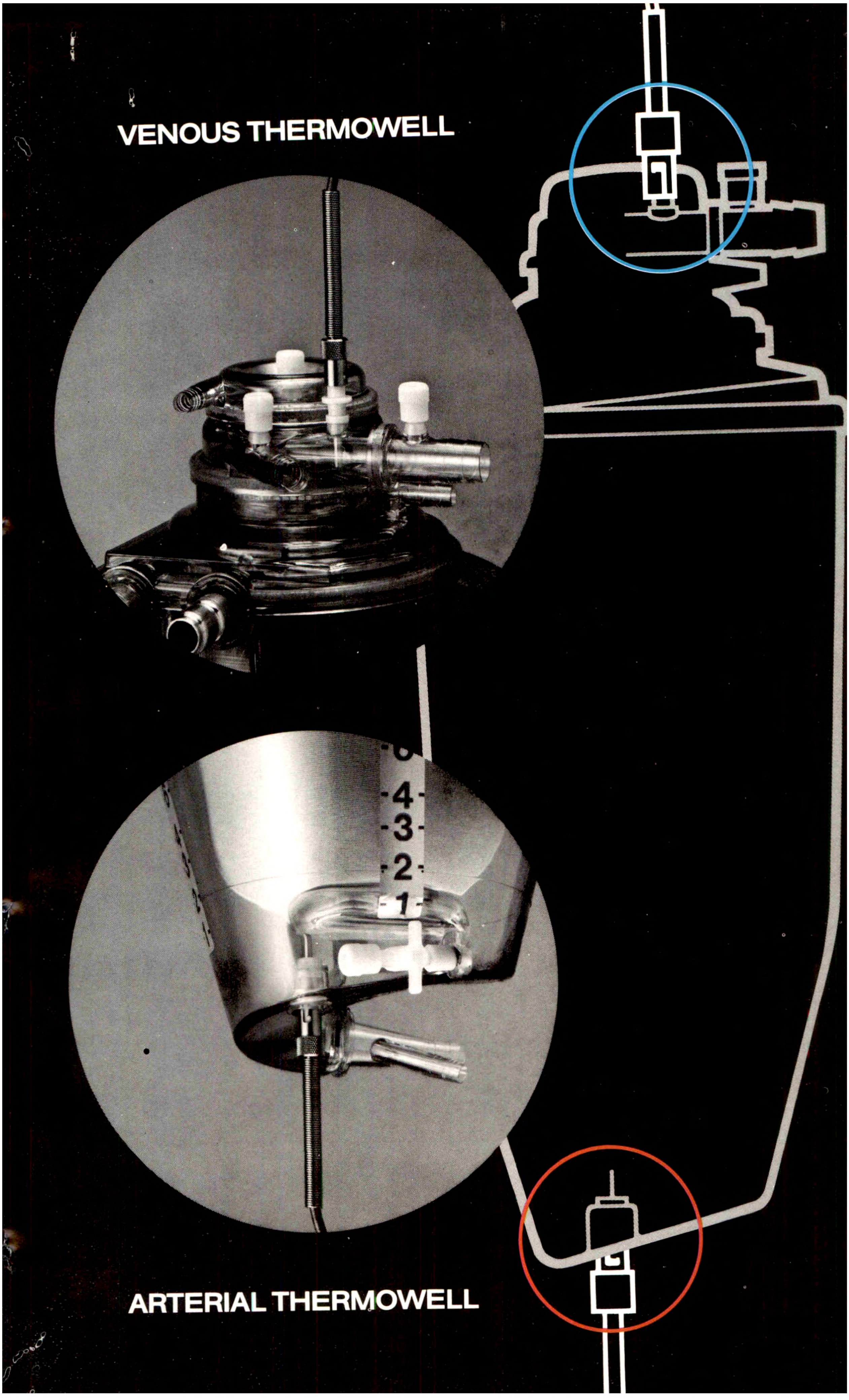
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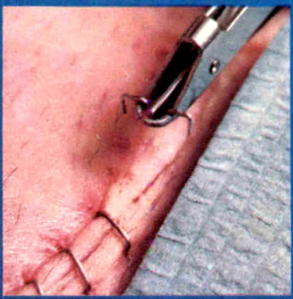

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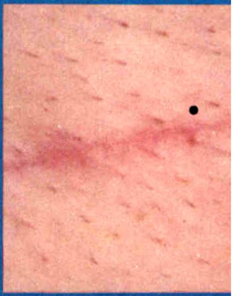
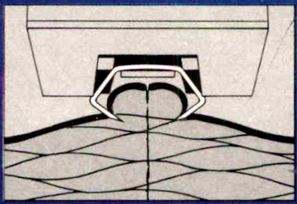
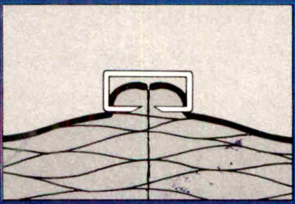




Touch skin lightly using centerline indicator and guide notch to ensure equidistant staple placement across the incision. Fire, release completely, and



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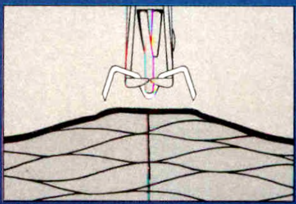

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Official Journal of The Society of Thoracic Surgeons
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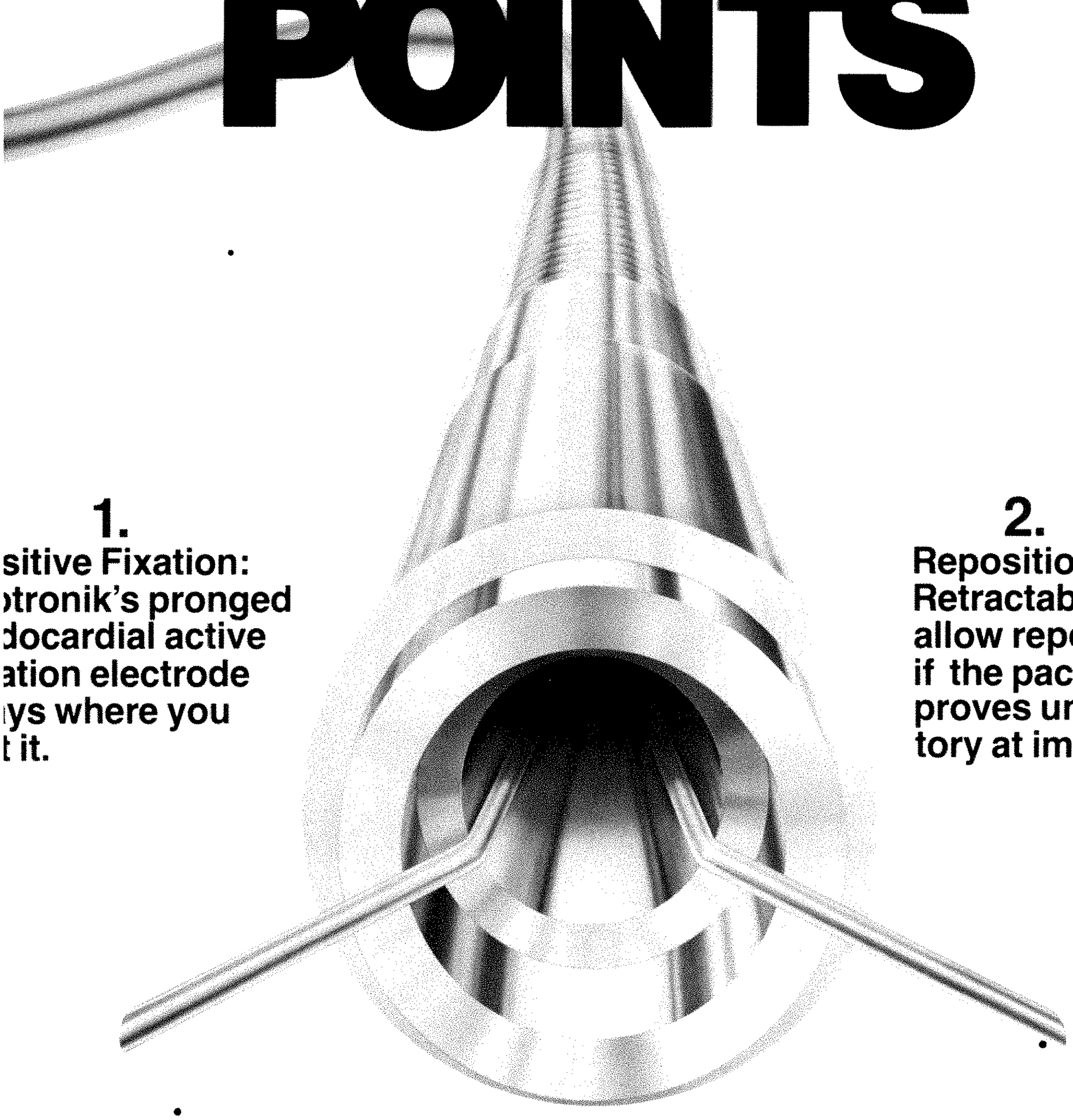

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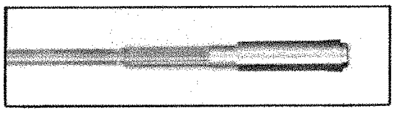

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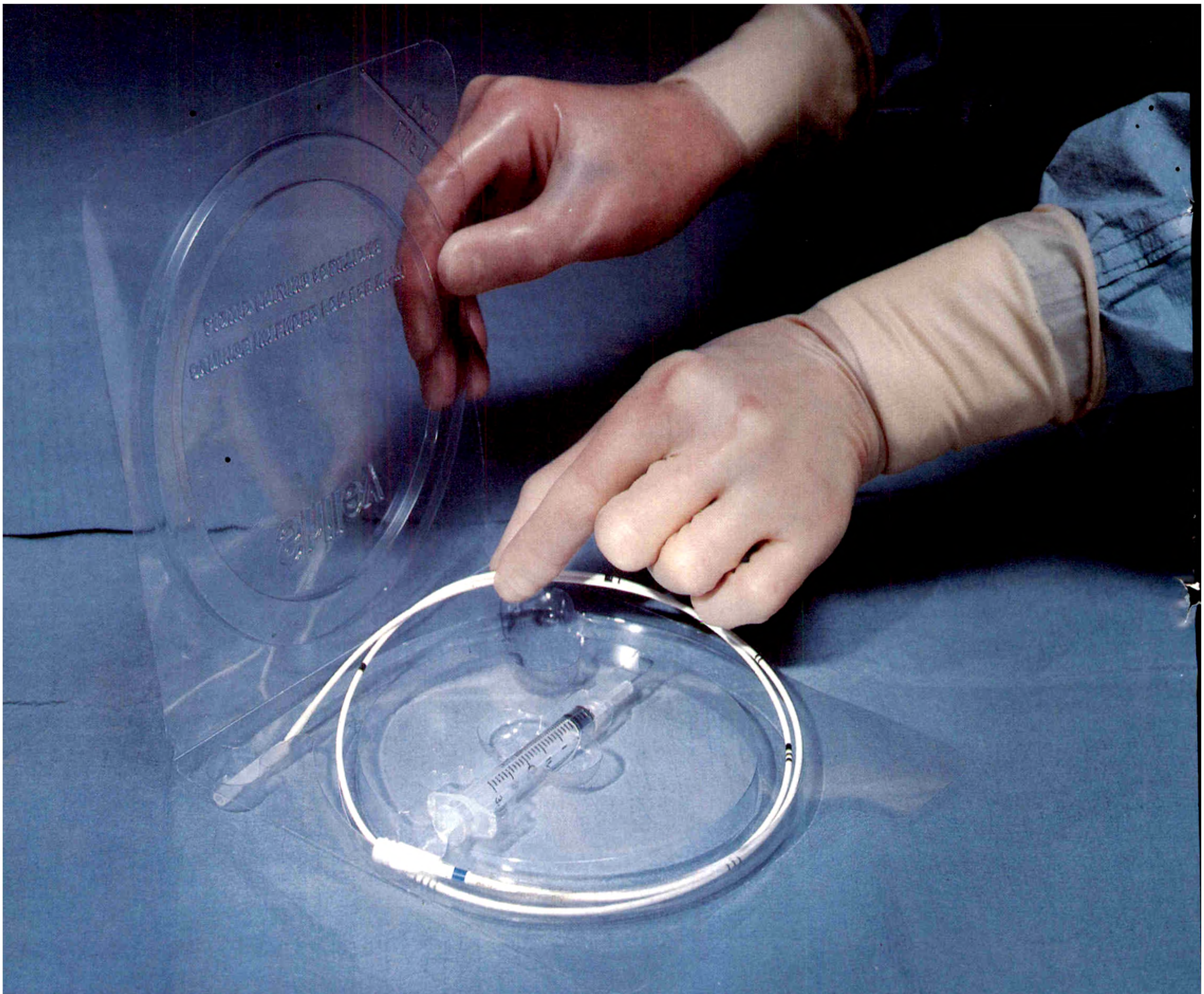

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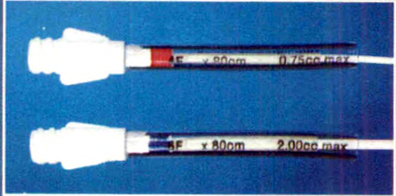

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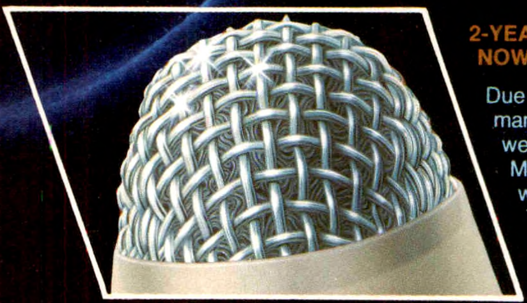

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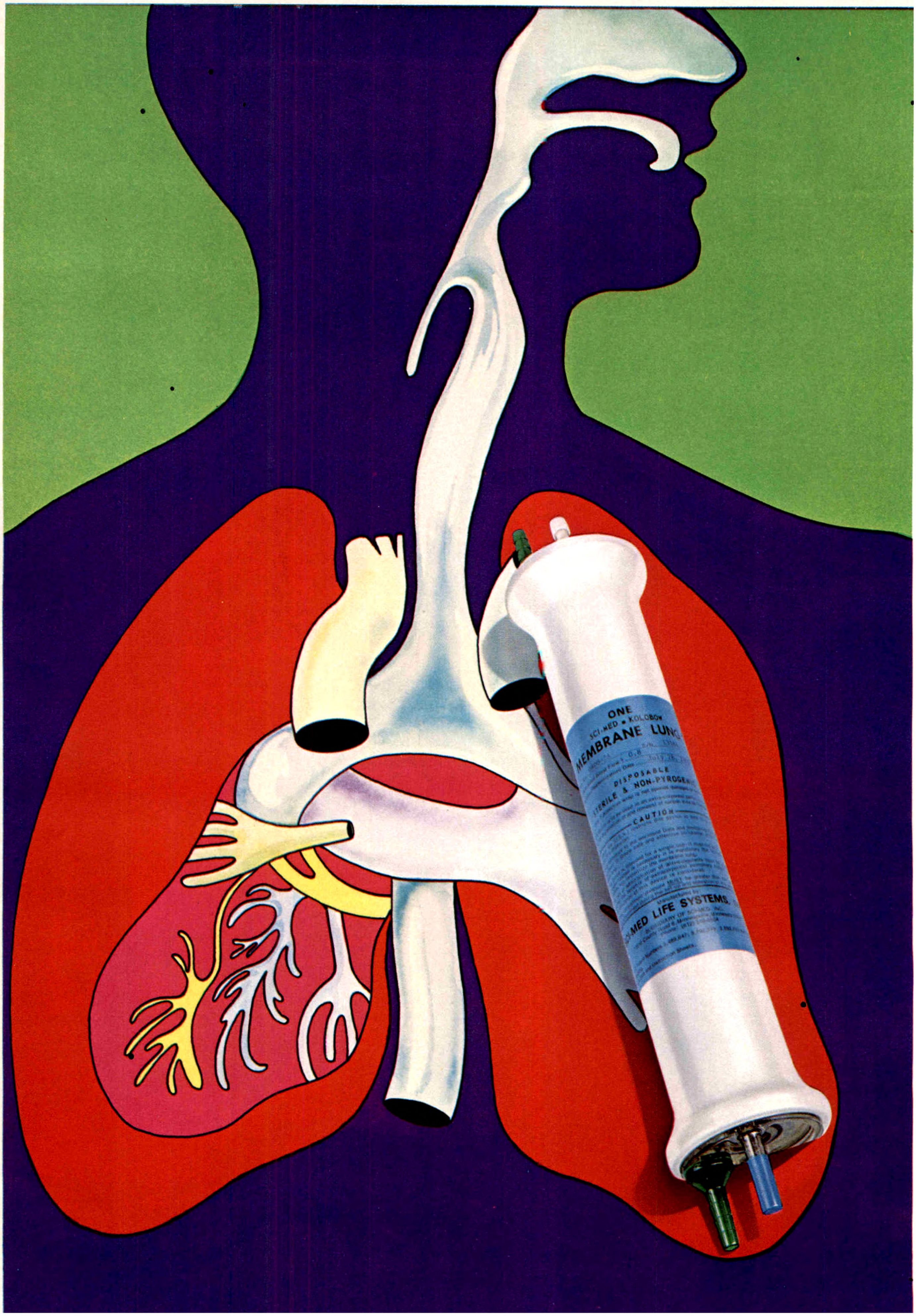
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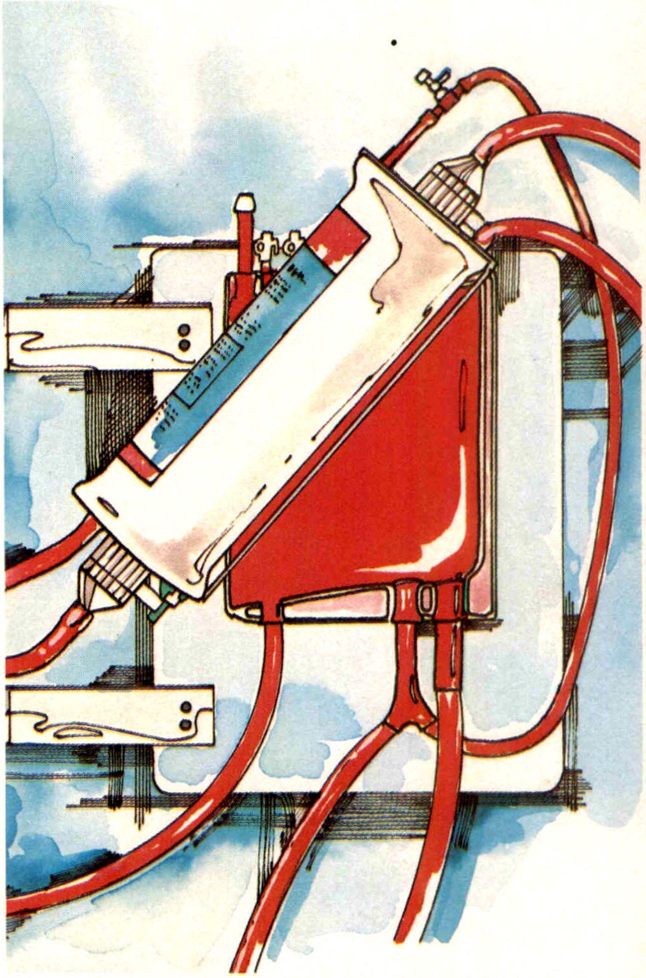

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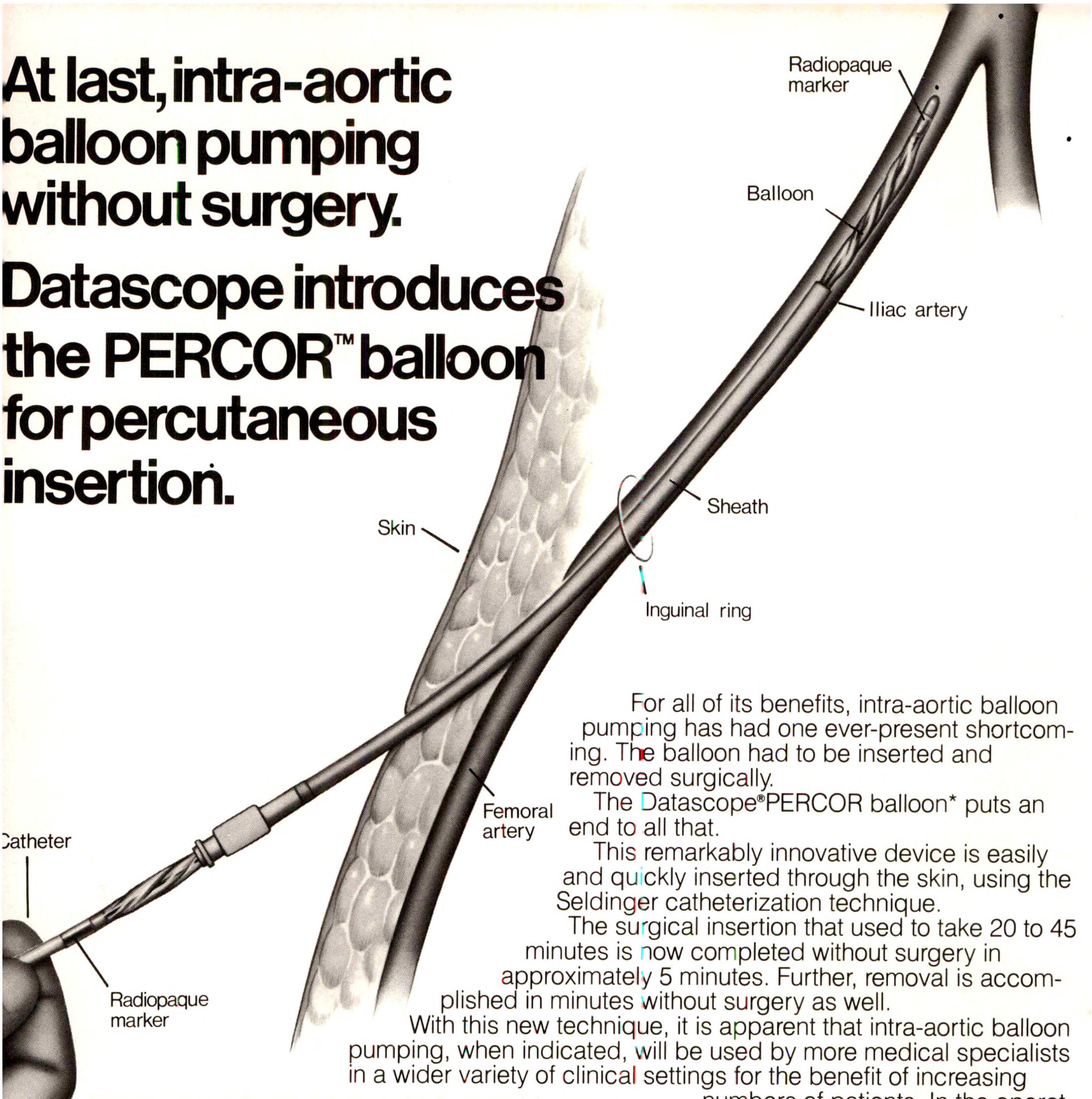

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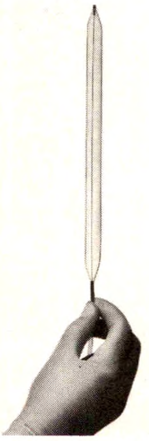

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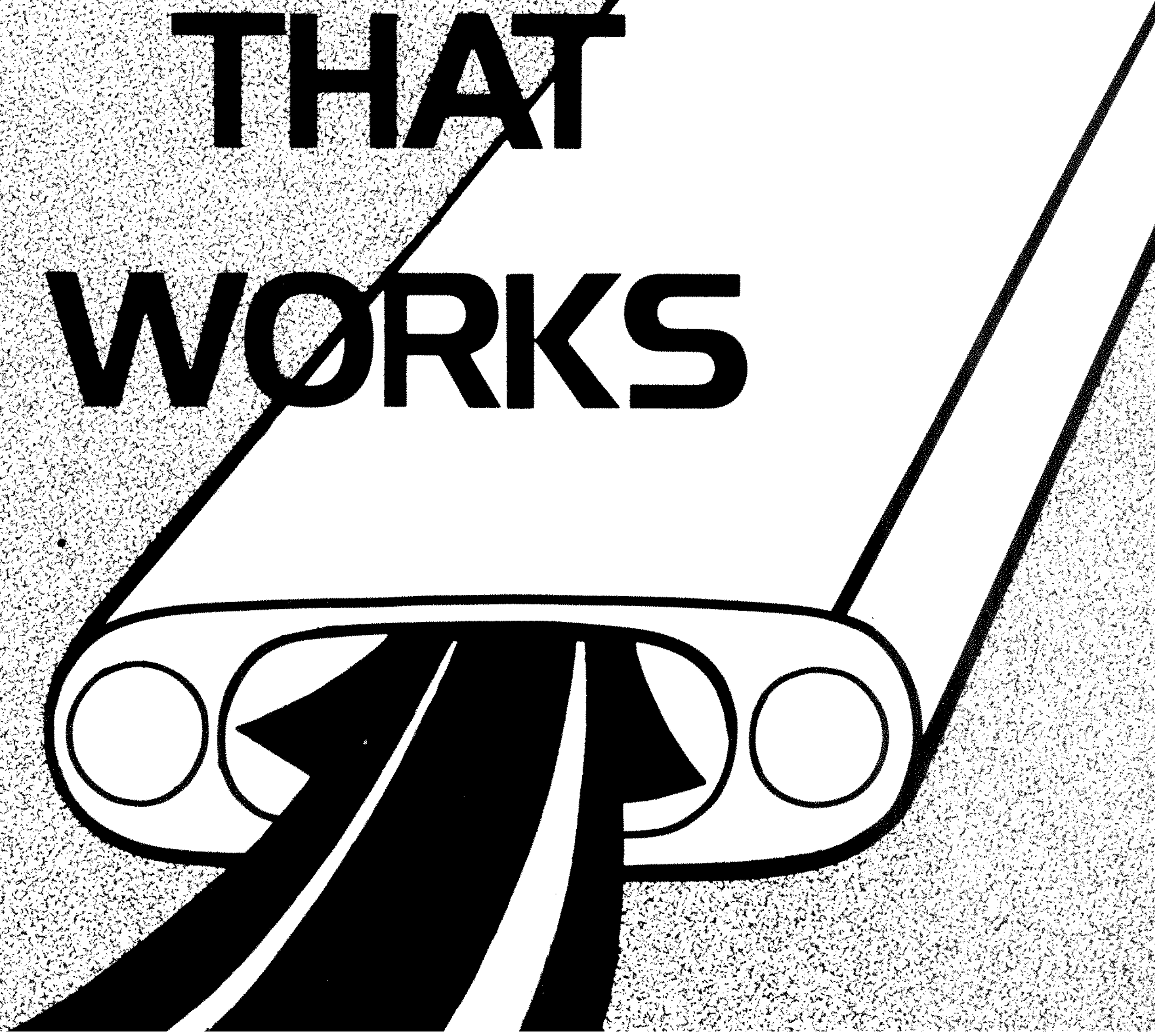

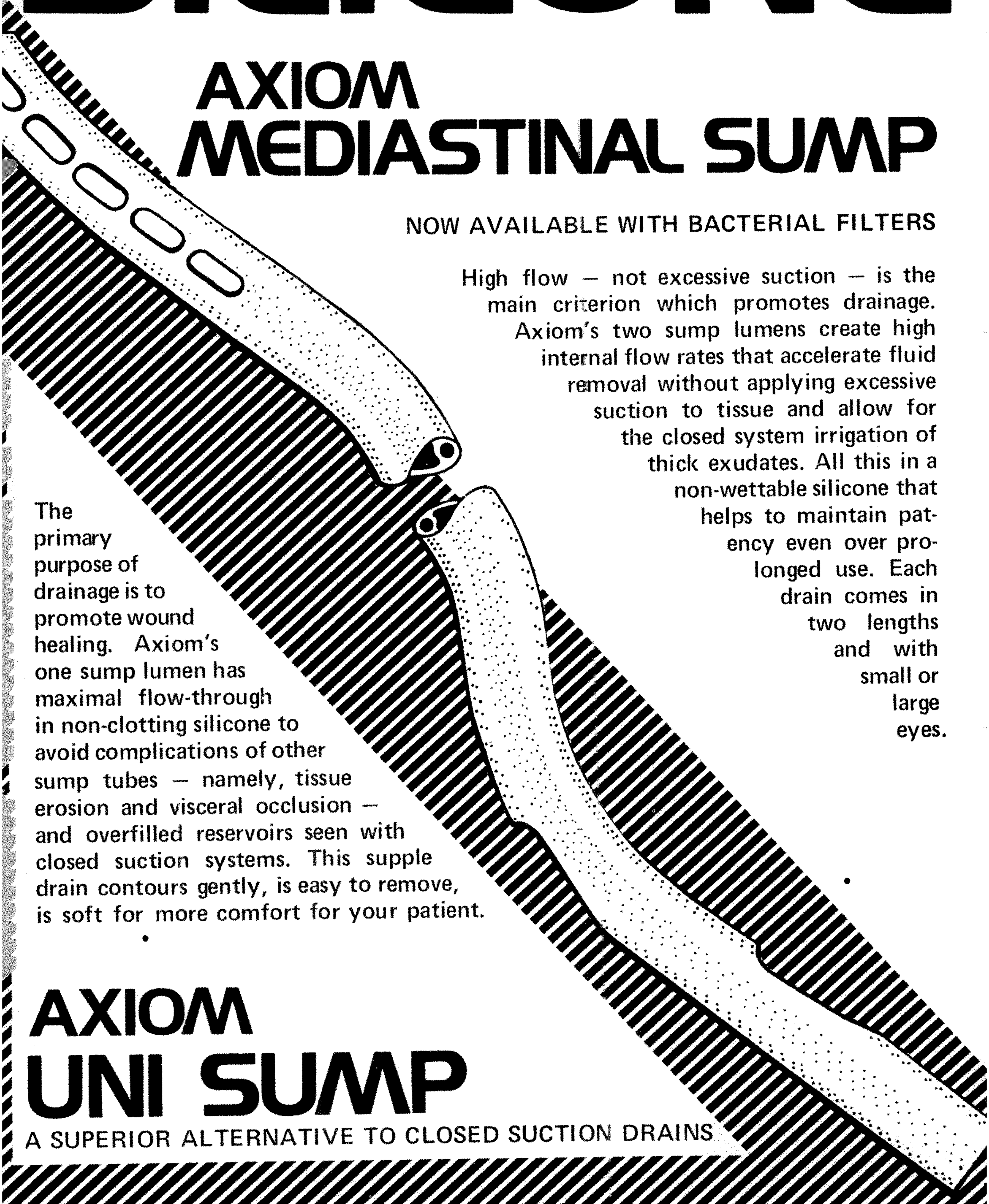

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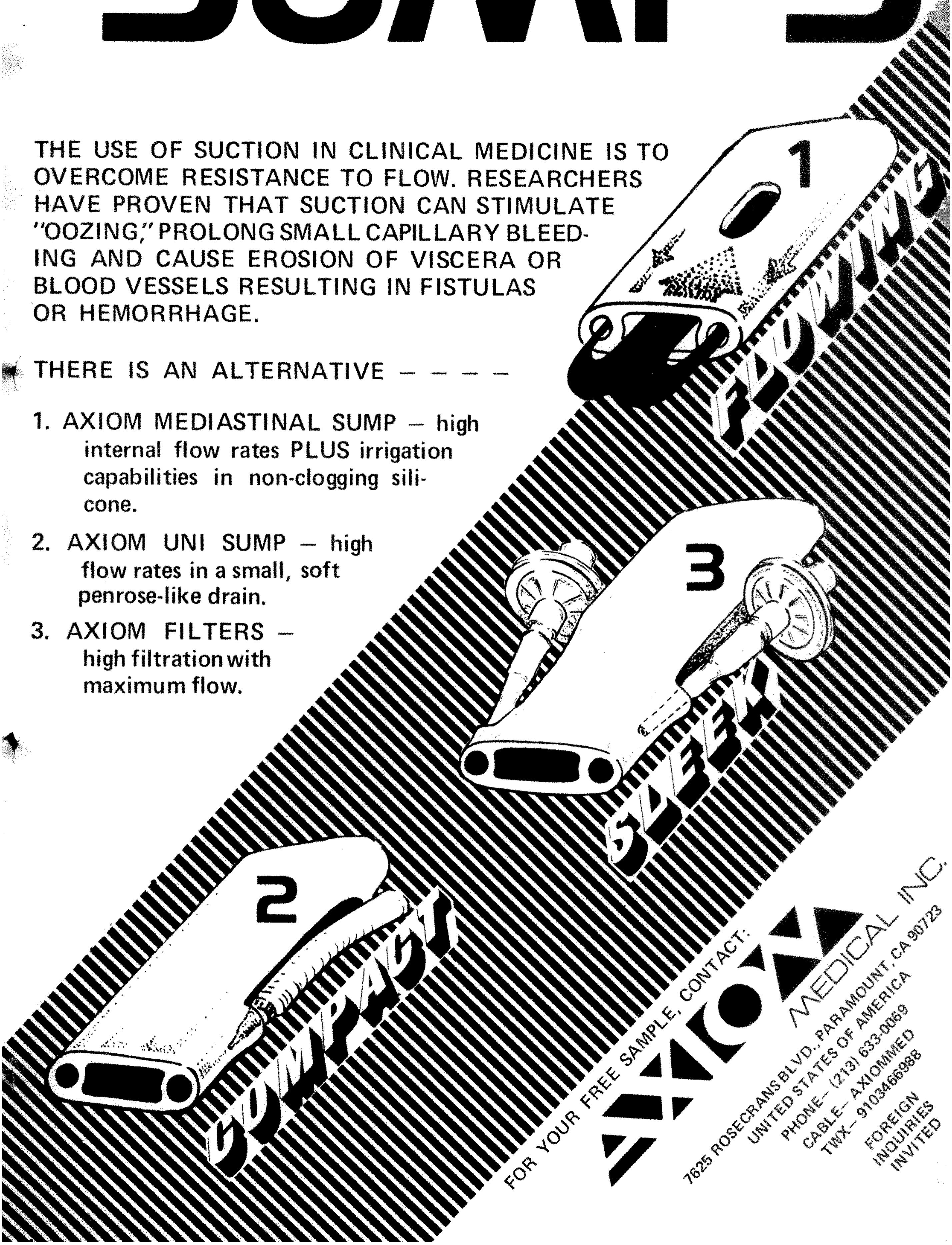

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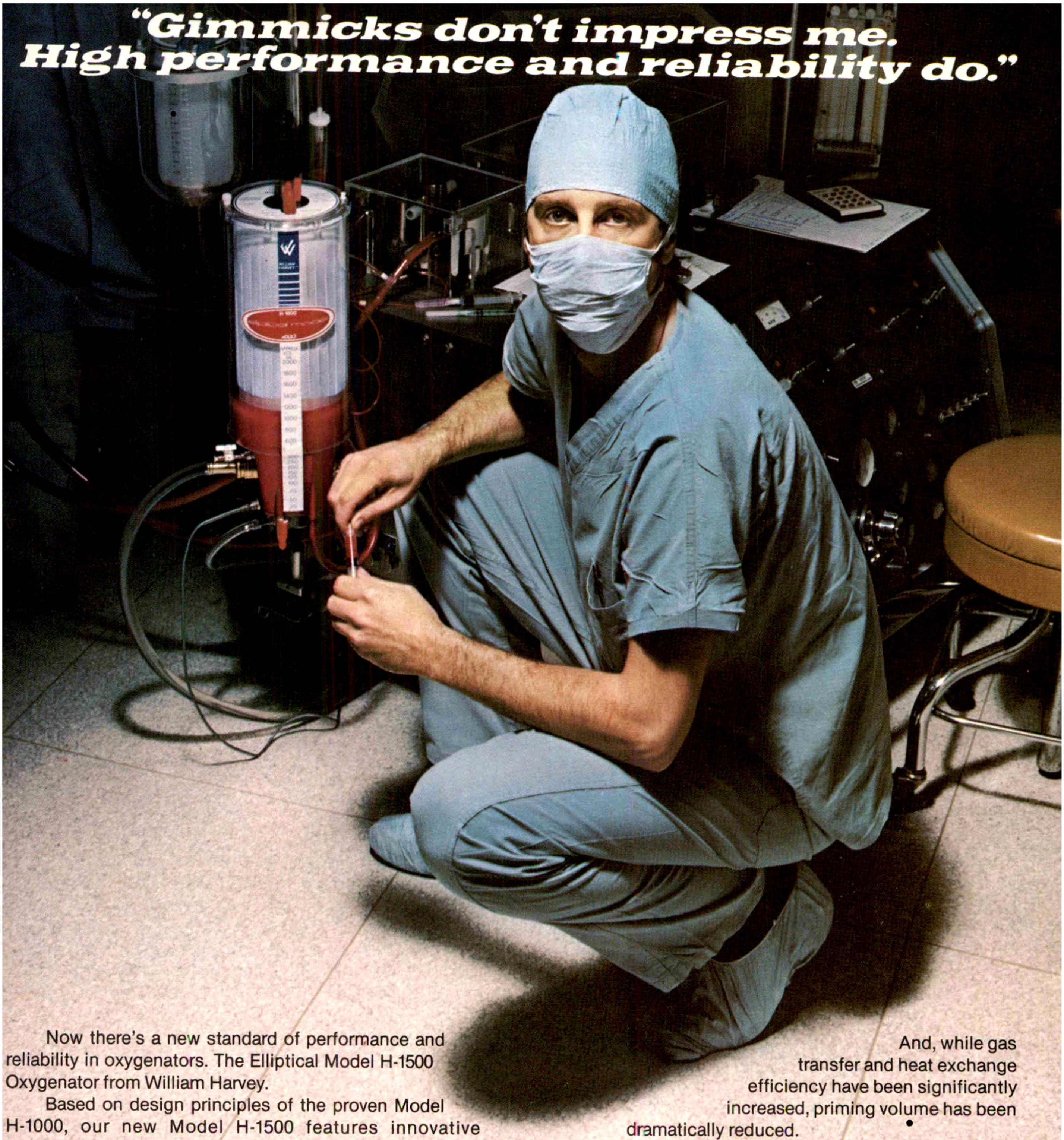
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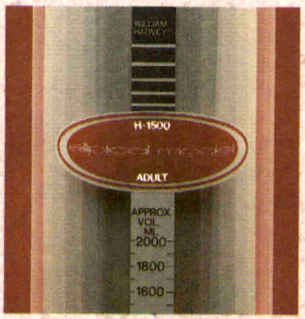

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The Reperfusion Injury of Cardiac Operation: Separating Myths from Realities

Bernadine H. Bulkley, M.D.

Achieving myocardial preservation by interventions aimed at protecting ischemic myocardium has been a major research goal of the past decade. The cardiologist can only envy the success of this effort in the operating room when it is contrasted with his struggle to preserve ischemic myocardium in the coronary care unit. Although in the operating room deliberate ischemia is imposed on the already oxygen-limited heart to achieve the necessary quiet operative field, the surgeon has the good fortune to be able to apply such potent myocardial preservatives as hypothermia and potassium arrest prior to the application of the controlled ischemic insult. The result has been a dramatic minimization and in some cases elimination of the cost of ischemia witnessed in the experimental laboratory and also in the human setting [1–3].

The study by Lolley and co-workers in this issue (p 110) focuses on one aspect of intraoperative myocardial preservation in humans. In a prospective clinical trial, they showed, in part, that a group of 263 patients undergoing cardiac operation with hypothermia and pharmacological cardioplegia combined with multiple aortic cross-clamping came away with good left ventricular function, a cardiac mortality of less than 1%, and an incidence of transmural myocardial infarction of less than 2%. The authors conclude that multiple aortic cross-clamping is no longer harmful to the heart and that the idea that added injury occurs due to intermittent reperfusion is a "myth."

The concern about multiple aortic cross-clamping is, of course, not a myth historically. Under conditions of normothermic anoxic arrest, intermittent reperfusion is associated with increased edema, more extensive contraction band or reperfusion necrosis, and worse left ventricular function when compared with continuous aortic cross-clamping [4, 5]. Since the intensity of the oxygen debt accrued during anoxic arrest has been dramatically alleviated by both hypothermia and pharmacological preservatives, it is not surprising that reperfusion injury, determined largely by the intensity of this debt prior to the reflow, would also be dramatically attenuated, if not eliminated [6]. Thus, the finding in the 263 patients in Group 2 supports the notion of Lolley and colleagues that the added damage resulting from multiple aortic cross-clamping may no longer be a reality or may be of such trivial amount as to be undetectable.

Does this human study show, as the authors conclude, however, that multiple aortic cross-clamping is superior to continuous cross-clamping? For a number of reasons, it does not. Some, albeit mild, amount of myocardial necrosis occurred in both groups in their study as indicated by the creatine phosphokinase (CPK) elevation; but the amount of necrosis between those patients in Groups 1 and 2 was strikingly similar as determined by the near identical levels of CPK (498.0 ± 55.2 IU versus 482.0 ± 33.2 IU, respectively) and CPK-MB (17.1 ± 1.05 IU versus 17.8 ± 0.71 IU, respectively). If myocardial necrosis was similar, then one must be cautious in attributing arrhythmias, pressor use, and poor outcome to "sequelae of myocardial necrosis," and should look for other explanations, in particular, for differences in cardiac death and in clinical "myocardial injury" (as defined as changes on electrocardiogram without enzyme abnormalities or poor clinical performance) between the patients managed with intermittent (Group 2) compared with continuous aortic cross-clamp (Group 1). One possible explanation arises if one looks separately at the

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patients with only coronary procedures and those with combined procedures.

For those having coronary bypass alone, there was no difference between the 183 patients in Group 1 and the 208 in Group 2 with regard to cardiac mortality—0.6% and 0.5%, respectively. Among the 89 patients having combined procedures, however, cardiac death was fifteen times greater in Group 1 (continuous cross-clamp) compared with Group 2 (intermittent cross-clamp), with mortalities of 26% and 1.8%, respectively ($p < 0.01$). New or deeper Q waves as one index of myocardial infarction were more frequent in the continuous cross-clamp group but this difference was not quite statistically significant. Since, again, the CPK release was similar between Groups 1 and 2, it is exceedingly difficult to attribute this rather high mortality of 26% in Group 1 to myocardial necrosis. A more overriding factor in the outcome between these two "combined" groups may be that the cardiac lesions and procedures performed were significantly different:

Combined Procedures (Total)	Group 1: Continuous (N = 34)	Group 2: Intermittent (N = 55)	Significance*
Mitral + coronary	17.6% (6/34)	16.3% (9/55)	NS
Aortic + coronary	20.6% (7/34)	21.8% (12/55)	NS
Aneurysm + coronary	44.1% (15/34)	58.2% (32/55)	NS
Multiple valves	17.6% (6/34)	1.8% (1/55)	$p < 0.05$
Valves + aneurysms + coronary	0	1.8% (1/55)	NS

*Chi-square analysis.

The tenfold differences in prevalence of multiple valve replacements in the group with continuous cross-clamp is significant ($p < 0.05$). As mortality would be higher for patients undergoing multiple valve replacement than the other combined procedures, the greater prevalence of a higher risk procedure in Group 1 can only lead to its higher mortality. Other such factors need also be sought for the close to 30% mortality of the 34 patients with combined lesions.

A major goal of clinical trials is to test and validate clinical concepts and, perhaps, separate myths from reality; but, such trials are a difficult challenge. In the design of a prospective clinical trial in which patients are randomized to two groups, it is necessary to assure a match between two arms of the study for those variables that might bias or obscure the outcome. A scheme of randomized stratification imposed on such a trial would assure that variables such as cardiac lesions, procedures undertaken, and, perhaps, surgeon or hospital of operation are evenly distributed in both groups. Another, even more troublesome, aspect of the clinical trial is the problem of numbers. The clinical trial should require a number of study patients sufficient to detect a real difference if it is present (low beta error) and to assure that if a difference is detected, it is statistically significant (low alpha error). One wishes to keep both the alpha and beta error low (< 0.05) to be convinced that observed differences are not merely a matter of chance [7]. The sample size required to keep these errors below 5% is, most importantly, related to the likelihood of the end point tested occurring and the anticipated treatment effect. For example, when mortality is an end point and mortality in the control population is high, then relatively few patients are needed to detect a given reduction in mortality. As the expected mortality in the control population declines, however, the number of patients necessary to detect a similar decrease in mortality in the study group increases *exponentially*. Thus, for an anticipated mortality of 50% in the control group, an intervention that decreases it by half could be detected in a total population of approximately 200 patients. If mortality in the control population is 6%, however, more than 3,000 patients are necessary to detect a halving of mortality [8]. With the low mortality of elective coronary bypass operation, even when combined with aneurysmectomy, it would be virtually impossible to detect a benefit for intermittent aortic cross-clamping unless a very large, perhaps multicenter study were performed. If the highest risk "combined" lesion group is to be studied, for example, the multiple valves, fewer study patients would be needed—but in the range of 100, and not the 7 studied here.

With these considerations, it becomes difficult to support the conclusions of Lolley and associates that the reperfusion injury of intermittent cardioplegia has become a myth, or the converse, that the protected anoxic heart benefits from intermittent reperfusion. The findings in this study can more convincingly be interpreted as showing that ischemic membrane damage was so minimal in Group 2 that the previously recognized insult of intermittent reperfusion was tolerated. If so, rather than disproving a myth, this study mainly reaffirms a reality: that biologically significant protection and preservation of ischemic myocardium in the majority of cardiac surgical patients have been achieved.

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The Treatment of Respiratory Paralysis by Diaphragm Pacing

William W. L. Glenn, M.D.

The article in this issue of The Annals (p 118) by Dr. Oakes and three of his colleagues entitled "Neurogenic Respiratory Failure: A 5-Year Experience Using Implantable Phrenic Nerve Stimulators" reports the experience at the Santa Clara Valley Medical Center in the management of respiratory paralysis by electrical stimulation of the phrenic nerves. Twenty stimulators were implanted in 11 patients, all presumably in the neck and when bilateral, at the same operation. All patients were tested before operation to demonstrate that phrenic nerve stimulation (transcutaneous or intravenous) could produce diaphragmatic contraction. No details are given on the characteristics of this response. In 13 of the implants, phrenic nerve stimulation (diaphragm pacing) was functioning well enough after 2 to 3 months to allow the patients to be off all other ventilatory support for at least 4 consecutive hours. Attempts at pacing in 7 patients failed to effect significant diaphragm activity.

Of 8 patients who had at least 1 successful stimulator implantation, 5 were shown in their follow-up period of 3 to 60 months (mean, 30.5 months) to have continuing benefit from stimulation; 2 of these patients were supported totally while 3 were supported at least 50% of the time. This meant they had many hours for rehabilitation and other activities untethered to a mechanical ventilator. Three other patients who apparently had been stimulated successfully in the early postoperative period were not still being stimulated at the time of the follow-up study. It was the authors' opinion that complete ventilatory independence should not be the criterion of success of chronic phrenic nerve stimulation in quadriplegic patients.

There is no question that part-time ventilatory support is worthwhile in the management and rehabilitation of these patients. The results in the Yale Clinic with treatment of 20 quadriplegic patients (37 stimulator implants) agree in most respects with those reported by Dr. Oakes and his co-workers. Two of our patients could not be paced effectively; in both, preimplant testing of the phrenic nerves by direct stimulation following their exposure had produced little or no response. Of 120 nerves in patients evaluated by transcutaneous phrenic nerve stimulation (TPNS), test data correctly predicted nerve viability and diaphragm function in 116. Four nerves subsequently shown to be viable could not be located by TPNS: 2 were in markedly obese patients and the other 2 were in an uncooperative child [9]. On the basis of this experience, I would not implant a stimulator in any patient in whom a normal phrenic nerve conduction time could not be demonstrated and vigorous contraction of the hemidiaphragm was not caused by either transcutaneous or direct stimulation. Transvenous stimulation of the phrenic nerve has not been in our hands a reliable indicator of the nerve's viability, especially on the left side.

As of April, 1980, 18 patients were paced for 3 months to 10 years. Seven (39%) were able to be supported totally by pacing. Two others were able to be fully supported but fatigue supervened after several months of continuous bilateral pacing. In 9 patients, pacing for periods of 9 to 17 hours (mean, 13.2 hours) a day was alternated with other methods of ventilatory support (Table 1) [1]. Thus, in 18 patients with viable phrenic nerves partial or full-time ventilatory support by diaphragm pacing was achieved. Ten patients died 10 months to six years after the start of pacing. In 7, death was unrelated to pacing. Of the 3 remaining patients, 1 died during sleep at home while an attempt was being made to wean her from the pacer. The 2 others were discharged with

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ventilation fully supported by continuous bilateral pacing. The development of diaphragm fatigue from continuous bilateral pacing necessitated their return to mechanical support. They died of respiratory complications after being returned to mechanical ventilation. It is apparent to me that pacing as has been practiced will provide for the total ventilatory need in only about 40% of patients with quadriplegia and respiratory paralysis. It does provide substantial palliation for most of the others.

A number of factors, either natural or iatrogenic, may be involved in our failure to achieve total ventilatory support in some quadriplegic patients. Obviously, if the injury to the cord involves the cell bodies of the phrenic nerves in the third to fifth cervical segments or the lower motor neurons of either phrenic nerve, maximal diaphragm function cannot be expected. Injury to the phrenic nerves from the operative procedure or from abnormal pressure caused by malposition of the nerve cuff, scar tissue, or infection has been observed. Failure to include in the neural cuff one or more accessory branches of the phrenic nerve may be a much more common cause of failure than we have heretofore appreciated. Finally, injury to the phrenic nerve or diaphragm by an excessive electrical charge applied to the phrenic nerve is a real possibility, as proved in the experimental laboratory [6].

During the past few years we have attempted to identify factors preventing optimum function of the diaphragm during long-term electrical stimulation of the phrenic nerve. In the experimental laboratory, we have studied the effect on tidal volume of current amplitude, waveform configuration, electrode configuration, pulse train repetition rate (respiratory rate), and stimulus frequency (pulse interval). The ideal parameters for electrical stimulation of the phrenic nerve were found to be submaximal current and slow pulse train repetition rate delivered at low frequency using a bidirectional waveform applied to the nerve through a monopolar electrode. Prior to transferring these laboratory findings to patients, we measured the effect of varying the current amplitude, rate of pacing, and stimulus frequency on tidal or minute volume in the quadriplegic patient. On the basis of these laboratory and clinical studies, we have revised the electrical parameters for stimulation, reducing the electrical charge to tissues to the lowest possible without jeopardizing ventilation. We now recommend for those patients whose ventilatory requirements can be satisfied by pacing, as evidenced by the maintenance of normal arterial blood gases, a stimulus frequency of 20 to 16.5 Hz (pulse interval of 50 to 60 msec), an inspiration duration of 1.3 seconds, a respiratory rate of 10 to 12 breaths per minute, and current amplitude set to effect just maximal or slightly submaximal tidal volume. Under no circumstances should the stimulus frequency be higher than 25 Hz (40 msec), the respiratory rate faster than 16 breaths per minute (except in the infant or small child), or the current amplitude higher than that which provides maximal tidal volume.

It may take 6 months or longer to condition the paralyzed diaphragm muscle [2, 6, 7] by pacing no matter what the schedule or mode (see Table 1). However, if ventilation can be supported only by bilateral simultaneous pacing, then an attempt must be made to convert the diaphragm muscle fibers to nonfatiguing fibers [6, 8]. This is done by gradually decreasing the frequency of the stimulation to 10 to 11 Hz (100 to 90 msec pulse interval), the respiratory rate to 8 to 10 breaths a minute, and the current amplitude to submaximal. Despite the use of these parameters, attempts to pace bilaterally full time have not yet been successful for more than a few weeks. Continued full-time pacing after the presence of fatigue is recognized is strictly contraindicated. It would result in permanent damage to the phrenic nerve and diaphragm [3, 5].* Some of the concerns and caveats applicable to diaphragm pacing are listed in Table 2 [1].

To overcome two other factors that might prevent optimal pacing, during the past three years we have used a monopolar electrode applied to the phrenic nerve. It is easier to apply, causes less trauma to the nerve, and is just as effective as the bipolar electrode. To

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*Ciesielski TE, Fukuda Y, Glenn WWL, et al: Response of diaphragm muscle to electrical stimulation of the phrenic nerve with high and low frequencies: a pathological study. (In preparation.)

Table 1. Mode and Time of Pacing in 20 Patients

Pacing Mode	Hours Pacing Each Mode	Total Hours Paced	Ventilatory Support in Patients		
			Full-Time	Part-Time	None
Unilateral alternating sides	8 to 12	24	5	0	0
Bilateral					
Continuous[a]	24	0	0	0	0
Alternating with other pacing modes	6 to 8	24	2	0	0
Alternating with other ventilatory support[b]	9 to 17	9 to 17	0	11	0
Pacing not effective	0	0	0	0	2[c]

[a] Bilateral continuous pacing was attempted in 5 patients, but was not successful for more than a few weeks due to development of fatigue regardless of the electrical parameters employed; we do not recommend that it be attempted.
[b] Pneumobelt, air sipping, mechanical ventilation, voluntary.
[c] Two patients in the series could not be paced effectively.

Table 2. Concerns and Caveats in Diaphragm Pacing

Concern	Caveat
1. Selection of patients for diaphragm pacing	Tantamount to successful ventilatory support by pacing is adequacy of structures to be affected by electrical stimulation.
2. Operative technique	Iatrogenic injury to phrenic nerve is most common cause of failure to pace a normal nerve. Infection of any of the implantable components usually requires removal of all.
3. Use of pacemaker	Lack of complete understanding of proper settings of electronic indicators can lead to inadequate pacing or irreparable damage to phrenic nerve and diaphragm.
4. Pacing schedule	The pacing schedule must be individualized for each patient's particular problem. Patients who require full-time pacing, particularly small children, will need day to day supervision for first 6 to 8 months of pacing.
5. Pacemaker apparatus	Pacemaker failure in a quadriplegic can be disastrous. A fail-safe alarm system must be available for patient to activate with head or tongue. Failure of pacemaker apparatus is most commonly due to: (1) battery failure; (2) broken antenna wire or connector; (3) component failure in implanted radio receiver; (4) circuit failure in exterior transmitter; and (5) electrode wire breakage, least likely. Failure to pace or pace properly may also be an indication of injury to nerve.
6. Upper airway obstruction and tracheal aspiration	Airway obstruction from several causes may interfere with ventilation. A clear airway during pacing is essential.
7. Sedatives, tranquilizers, narcotics	Any respiratory depressant is contraindicated. Pacing alone will not support ventilation in the sedated patient.
8. Major operations or disease, respiratory complications, terminal illness that affects the body as a whole	Pacing may not provide sufficient ventilatory support in disorders that stimulate or depress general body metabolism.
9. Fatigue of diaphragm	Fatigue of diaphragm results in inadequate ventilation and, if persistent, irreparable damage to nerve and diaphragm. The diaphragm must be rested by providing passive ventilation should fatigue occur and then pacemaker indicators and schedule must be readjusted.

eliminate the failure to include an accessory branch of the phrenic nerve (reportedly present in 75% of patients [4]) in the electrode cuff, we now recommend the transthoracic approach to the phrenic nerve for implanting the electrode in all quadriplegic patients, and also in those patients with central alveolar hypoventilation who require maximal diaphragm excursions while on pacing. The implants are placed at separate operations, as is the case when the implants are made on the nerves in the neck, approximately two weeks apart. My colleagues and I believe that as a result of recent clinical and laboratory experience mentioned here, it is now possible to improve the efficiency of diaphragm pacing.

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ORIGINAL ARTICLES

Is Reperfusion Injury from Multiple Aortic Cross-Clamping a Current Myth of Cardiac Surgery?

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ABSTRACT **Four hundred eighty adult patients undergoing cardiac operations had systemic and topical hypothermic anoxic arrest supplemented with potassium chloride pharmacological cardioplegia in a prospective randomized study. Group 1 (217 patients) had continuous aortic cross-clamping and one single anoxic arrest period during the cardiac portion of the operation, which resulted in a transmural myocardial infarction rate of 8.3%, myocardial "injury" incidence of 12.4%, 4.6% cardiac-related deaths, 11.5% and 24.8% severe and malignant ventricular arrhythmias, 21.7% rate of severe vasopressor usage, a mean group serum glutamic oxaloacetic transaminase (SGOT) of 140 ± 39 IU, and a mean group lactic dehydrogenase (LDH) of 636 ± 78.2 IU. Group 2 (263 patients) had intermittent aortic cross-clamping with multiple reperfusion intervals, which resulted in a significantly lower incidence of transmural myocardial infarction at 1.9% ($p < 0.01$), rate of myocardial injury at 5.66% ($p < 0.02$), number of cardiac deaths at 0.76% ($p < 0.02$), 8.7% and 16.0% severe and malignant ventricular arrhythmias ($p < 0.01$), severe vasopressor utilization rate of 14.3% ($p < 0.05$), mean group SGOT at 72.0 ± 3.1 IU ($p < 0.01$), and mean group LDH at 471.0 ± 12.3 IU ($p < 0.05$) than Group 1. These results do not support the contention that intermittent aortic cross-clamping in conjunction with hypothermia and pharmacological cardioplegia leads to increased clinical cardiac damage compared with continuous aortic cross-clamping. The converse is implied, in that the anoxic heart may benefit from the physiological effects of briefly reperfused oxygenated blood.**

With the advent of cardiac hypothermia and pharmacological cardioplegia, workers in many centers have advocated the use of prolonged uninterrupted anoxic cardiac arrest utilizing one period of aortic cross-clamping without interval reperfusion during cardiac surgery [1, 2, 4, 5, 11, 12, 14]. Intermittent aortic cross-clamping, in spite of its being the time-honored method of cardiac preservation [20], has been abandoned, presumably to avoid increased reperfusion edema and injury alleged to occur after multiple perfusion intervals. This new approach is based on the belief that the summation of cardiac injury sustained during multiple cross-clampings and brief reperfusion intervals is greater than that occurring for the same anoxic arrest time during continuous aortic cross-clamping [1, 4, 7, 8].

Some of the clinical reports in support of this concept are based on sequential series that are not comparable because of continued advancement of the "state of the art" [1, 11, 14]. These studies have usually compared hypothermic, continuously cross-clamped, anoxic arrested hearts to normothermic, fibrillating hearts or normothermic, intermittently arrested hearts with interval fibrillation [7, 8, 11, 12, 14]. Hearts treated with hypothermic pharmacological cardioplegia and subjected to continuous aortic cross-clamping have likewise been compared to normothermic, fibrillating, unclamped hearts, to normothermic, intermittently cross-clamped hearts with interval fibrillation, or to intermittently cross-clamped hearts with hypothermia and interval fibrillation [1, 2, 5]. In none of these clinical studies were myocardial preservation factors kept constant while intermittent cross-clamping alone was varied with continuous cross-clamping.

Most of the laboratory experiments have been patterned after clinical reports and are lacking in the same respects or else involve extreme

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conditions in which animals having intermittent cross-clamping were subjected to repeated and prolonged anoxic or ischemic arrest periods at normothermia with high-pressure reperfusion intervals and normothermic, fibrillating hearts [4, 7, 8, 16]. No studies have compared intermittent to continuous aortic cross-clamping utilizing modern pharmacological cardioplegia, hypothermia, and avoidance of gross interval fibrillation. Only Follette and associates [10] have conducted a relatively comparative experiment; this was in their study on "blood cardioplegia," which may be considered a modified form of intermittent aortic cross-clamping. There is evidence that hypothermia, when combined with intermittent aortic cross-clamping, noticeably reduces reperfusion injury occurring during normothermic intermittent cross-clamping [3]. In addition, it is known that potassium chloride cardioplegia with substrate, hyperosmotic cardioplegia, and coronary arterial infusates also can negate reperfusion edema [9, 15, 21].

Because these factors have not been studied in combination with one another, it became imperative that a clinical study be conducted to compare intermittent with continuous aortic cross-clamping utilizing a modern form of pharmacological cardioplegia, which includes base, potassium chloride, an osmotic agent, and metabolic substrate. Therefore this study was undertaken to see whether brief multiple reperfusion periods with oxygenated blood were clinically harmful to the anoxic arrested heart compared with hearts made anoxic by continuous aortic cross-clamping. Clinical harm was assessed by the incidence of myocardial necrosis sequelae such as transmural myocardial infarction, myocardial "injury" pattern, cardiac-related death, and elevated cardiac enzyme levels, and by rates of atrial arrhythmias, severity of ventricular arrhythmias, utilization of vasopressors to keep blood pressure within a preassigned range, and incidence of low cardiac output syndrome necessitating intraaortic balloon support. Diminution of the relative risk of cardiac surgery through anoxic arrest imposed by either continuous or intermittent aortic cross-clamping could be assessed by reduced incidences of these occurrences. In a practical sense, this improvement would be evident in better clinical cardiac function and lessened evidence of myocardial necrosis.

Material and Methods

Four hundred eighty adult patients undergoing cardiac operations were initially assigned in a random fashion to two groups that differed as to whether intermittent aortic cross-clamping was employed during procedures utilizing anoxic cardiac arrest. These patients included all those having elective or urgent operations during which aortic cross-clamping is commonly interrupted to allow interval reperfusion periods, such as multiple coronary artery bypass grafting, multiple valve replacement, coronary artery bypass plus cardiac valve replacement or ventricular aneurysm repair, or combinations of these procedures. Instances of emergency salvage, acute myocardial infarction, and procedures for which it is a common practice to employ one aortic cross-clamping, such as single coronary artery bypass grafting, ventricular aneurysm resection, or single valve replacement, were not included in the series. The study was prospective and included the period January, 1977, through January, 1979.

In Group 1 (217 patients), the aorta was cross-clamped continuously without reperfusion intervals before final release of the clamp, and the patients had one uninterrupted anoxic period for completion of the cardiac procedure. The 263 patients in Group 2 had the aorta cross-clamped intermittently with multiple reperfusion intervals before final release of the clamp at completion of the cardiac portion of the operation and of the anoxic arrest periods. Usually distal coronary arterial grafts were done in sequence, allowing 3- to 5-minute perfusion intervals between each anastomosis. For more extensive procedures with anoxic arrest periods longer than 30 minutes, such as valve replacements in combination with coronary, aneurysm, or other valve procedures, 15- to 20-minute reperfusion intervals were employed between major portions of the cardiac procedure and anoxic arrest times. During the brief reperfusion periods, hearts usually remained in standstill with minimal stiffening and fasciculation.

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Coronary arterial perfusion with oxygenated pump blood was not utilized during aortic valve procedures in either group. Cardiopulmonary bypass was carried out according to standard techniques, utilizing systemic (25° to 28°C) and topical (iced saline slush at 4° to 7°C) hypothermia in the pericardial well, cold cardiac standstill, and routine venting of the left ventricle if left atrial pressure rose above 20 mm Hg. The pump perfusate was Normosol-R (pH 7.4) containing 4 mEq of potassium chloride per liter. The hemodilution factor was 16 ml per kilogram of body weight. A bubble oxygenator and roller pump were utilized, with high-flow perfusion of 70 ml per kilogram and maintenance of mean preoperative arterial pressure for standard operations judged not to involve more than 60 to 90 minutes of cardiopulmonary bypass time. For extended procedures a membrane oxygenator was employed. Perfusion pressures ranged from 65 to 90 mm Hg and were not allowed to exceed 100 mm Hg. Distal anastomoses were performed before proximal anastomoses. Warming was effected during the last aortic cross-clamping, at the beginning of the last anastomosis, or during closure of the heart or aorta, and immediate defibrillation was accomplished, either spontaneously or electrically, as soon as the aortic cross-clamp was released. Central venous, left atrial, and arterial pressures were monitored and kept within preoperative or physiological range.

All patients in both groups had the aortic root cannulated with a large-bore 12F polyethylene catheter, through which a solution of 1,000 ml of 5% glucose in water containing 20 mEq of potassium chloride, 4.4 mEq of sodium bicarbonate, 12.5 gm of mannitol, and 20 units of regular insulin was infused at the beginning of the aortic cross-clamping. The solution was injected in a 200 ml bolus over a 1- to 2-minute interval and subsequently allowed to drip in continuously, under gravity pressure (in line, 40 mm Hg), at a rate of 300 ml every 15 minutes throughout the duration of aortic cross-clamping. This was repeated for each cross-clamp period or at 15- to 20-minute intervals during continuous aortic cross-clamping. In operations involving an opened aortic root, the solution was infused or dripped in through cannulas loosely inserted in the coronary artery orifices. The clear solution escaping around the loosely applied cannulas did not interfere with performance of the procedure; and because of the low viscosity of the asanguineous solution, little holding or infusion pressure was needed to infuse the coronary circulation effectively, thereby avoiding damage to the coronary arteries. The rationale for these approaches was that after the initial bolus of solution was administered to achieve a flaccid and electromechanically quiescent heart, a continuous drip could replenish anaerobic substrate (since a form of "multidose" cardioplegia would keep the heart electromechanically quiescent) and achieve coronary washout of lactic acid and anaerobic intermediate metabolites to maximize glycolytic flux. A mean volume of 1,250 ml per patient was utilized (range was 450 to 2,500 ml). The solution had a pH of 7.78 and osmolality of 348 mOsm, and was at 4°C.

As the study progressed, individual surgeon preference was established in extensive procedures, and critically ill poor-risk patients were assigned to intermittent aortic cross-clamping in violation of the protocol. This biased the study against Group 2 by enlarging its numbers to include patients in New York Heart Association Functional Class 4 and Canadian Heart Association Angina Class 4. Including a larger number of worse cases in Group 2 should have resulted in greater evidence of poorer postoperative clinical performance. The contrary occurred in this group, indicating that useful information was available in the study despite a break in the randomization process.

The need for vasopressor (dopamine) to maintain postbypass pressures above preoperative levels or at 120 mm Hg systolic in the later recovery period was observed and recorded. Subsequent vasopressor usage was quantitated according to the following schedule: none if the patient had postbypass pressures above either 120 mm Hg systolic or the preoperative mean aortic pressure and required no dopamine; mild if the patient subsequently utilized less than 0.6 μg of dopamine per kilogram per minute at any time; and severe if the patient needed more than 0.6 μg of dopamine per kilogram per minute to maintain a pressure greater than 120 mm Hg systolic or the preoperative mean aortic pressure. Perfusion pressures were kept at this range in the belief that higher levels would aid in preventing thrombosis of fresh grafts.

Arrhythmias were observed and recorded for at least five days postoperatively using a Hewlett-Packard Model HP-782-20B computerized arrhythmia monitoring system. Atrial arrhythmias were graded as follows: none if the patient had no atrial disturbances other than an occasional paroxysmal atrial contraction (PAC); mild if the patient experienced an episode of paroxysmal atrial tachycardia (PAT), atrial flutter, or atrial fibrillation that was hemodynamically minor, lasted less than one day, and resolved on minimal drug therapy; and severe if an episode of PAT, atrial fibrillation, or atrial flutter resulted in hypotension, lasted more than one day, or necessitated extensive drug intervention, electrical cardioversion, or both. Ventricular disturbances were graded as follows: none if no paroxysmal ventricular contractions (PVCs) occurred; mild if PVCs occurred but were unifocal and no greater than 10 per minute; severe if the patient had episodes of multifocal PVCs, PVCs greater than 10 per minute, or events such as bigeminy, trigeminy, or paired PVCs; and malignant if the patient had an episode of salvos of PVCs, ventricular tachycardia, or ventricular fibrillation.

Serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH), and creatine phosphokinase (CPK) were monitored 12, 24, and 48 hours postoperatively, and peak levels were recorded. Heart muscle band fraction (CPK-MB) was monitored every 8 hours for 48 hours, and peak levels were compared between the two groups. The myocardial infarction index for each patient was computed from these values according to the method of Shell and Sobol [18, 19], and the mean group levels were compared. Because patients with acute infarction were excluded from the study, preoperative enzyme levels in the two groups were normal and similar. In Group 1, preoperative mean enzyme levels were 23.2 ± 1.28 international units (IU) for SGOT, 166 ± 4.48 IU for LDH, and 32.9 ± 3.14 IU for CPK. Mean preoperative enzyme levels in Group 2 were 20.1 ± 1.12 IU for SGOT, 168 ± 4.29 IU for LDH, and 43.85 ± 8.1 for CPK.

The incidence of unequivocal transmural myocardial infarctions was recorded. This was assessed postmortem or by the appearance of new or deeper Q waves (greater than 2 mm depression) on two subsequent postoperative electrocardiograms with SGOT or CPK-MB above 100 IU. Myocardial injury or damage was also assessed and was assumed to have occurred if electrocardiographic changes such as currents of injury were observed but were unassociated with enzyme changes, if enzyme changes were detected without electrocardiographic changes, or if clinical cardiac performance was poor. The need for intraaortic balloon counterpulsation to counteract low cardiac output syndrome was recorded, as was the incidence of cardiac-related deaths. Group mean values were compared statistically by means of Student's *t* test. The incidence of cardiac-related events was compared using chi-square contingency tables.

Results

The two groups established for this study were of similar mean age: 57.0 ± 0.7 years for Group 1 and 57.0 ± 0.6 years for Group 2 (all group means are given with standard error of the mean). Group 1 had 23.0% female patients (50 of 217) and Group 2 had 23.6% (62 of 263 patients). Because of the protocol violations that resulted in more clinically poor risk patients in Group 2, that group had a higher incidence of preoperative myocardial infarction (63.9%; 168 of 263 patients) than Group 1 (40.1%; 87 of 217 patients). Mean percentage left ventricular ejection fractions in Group 2 were somewhat lower, at 59.0 ± 1.0%, than in Group 1, 62.0 ± 1.2%. Left ventricular end-diastolic pressures were similar for the two groups: 14.0 ± 0.6 mm Hg in Group 1 versus 15.0 ± 0.6 mm Hg in Group 2.

Of 183 Group 1 patients undergoing coronary artery bypass, 4, 35, 111, and 33 were in Canadian Heart Association* Angina Classes 1, 2, 3, and 4, respectively; in Group 2, 0, 28, 104, and

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*Canadian Heart Association angina classification: Class 0—no angina pectoris; rest, 0; Class 1—angina only with strenuous or prolonged activity; rest, 0; Class 2—angina with rapid walking up stairs or uphill, with cold, or with emotion; rest, 0; Class 3—angina with walking one to two blocks or a flight of stairs; rest, 0; Class 4—angina with any physical activity; rest, 0. (From the Canadian Cardiovascular Society Committee: Nomenclature and Grading for Coronary Artery Surgery, 1972.)

Table 1. Total Cardiac Procedures Performed in the Two Groups of Patients

Procedure	Group 1: Continuous Cross-clamping	Group 2: Intermittent Cross-clamping
Double bypass	43	39
Triple bypass	96	86
Quadruple bypass	42	69
Quintuple bypass	2	11
Sextuple bypass	0	3
Mitral and coronary	6	9
Aortic and coronary	7	12
Ventricular aneurysm and coronary	15	32
Multiple valves	6	1
Valve, aneurysm, and coronary	0	1
Total patients	217	263

76 of 208 patients were in Canadian Heart Association Classes 1 through 4. Of 34 Group 1 patients having combined procedures, 0, 7, 18, and 9 were in New York Heart Association* Functional Classes 1, 2, 3, and 4, respectively, before operation; of the 55 in Group 2, 0, 9, 20, and 26 were in Functional Classes 1, 2, 3, and 4. The range of cardiac procedures was similar in both groups (Table 1). There were more multiple valve procedures in Group 1, but Group 2 patients had more quintuple and sextuple coronary artery bypass graftings and combined coronary artery bypass with cardiac valve or aneurysm repair or both.

Group 1 had a mean total cardiopulmonary bypass time of 93.0 ± 2.5 minutes (range, 47 to 292 minutes), significantly ($p < 0.001$) shorter than the time of 110.0 ± 2.4 minutes (range, 48 to 274 minutes) in Group 2. This reflects the added reperfusion time during intermittent aortic cross-clamping in Group 2. However, the mean aortic cross-clamp time for Group 1, 52.0 ± 1.3 minutes (range, 22 to 144 minutes), was nearly the same as that for Group 2, 50 ± 1.0 minutes (range, 20 to 112 minutes), indicating that anoxic arrest time was not prolonged when intermittent aortic cross-clamping and pharmacological cardioplegia were utilized. The incidence of immediate spontaneous defibrillation was similar in both groups: 52% (113 of 217 patients) for Group 1 and 58% (152 of 263 patients) for Group 2.

Group 2, despite having a longer cardiopulmonary bypass time, had a significantly lower ($p < 0.01$) mean peak SGOT than Group 1, 72.0 ± 3.1 versus 140.0 ± 39.0 IU. The mean peak LDH of 471.0 ± 12.3 IU in Group 2 was significantly lower ($p < 0.05$) than the 636 ± 78.2 IU in Group 1. However, Group 1's postoperative mean peak CPK (498.0 ± 55.2 IU), CPK-MB (17.1 ± 1.05 IU), and CPK-MB myocardial infarct index (8.2 ± 0.6 gram-equivalents) were similar to the Group 2 mean peak CPK (482.0 ± 33.2 IU), CPK-MB (17.8 ± 0.71 IU), and CPK-MB myocardial infarct index (8.1 ± 0.4 gram-equivalents). Group 1 patients demonstrated a significantly higher incidence of myocardial necrosis sequelae by having more transmural myocardial infarctions ($p < 0.01$), instances of myocardial injury ($p < 0.02$), and cardiac-related deaths ($p < 0.02$) (Table 2). This trend was even more striking for the subgroup of patients having multiple, extensive procedures such as combined coronary arterial bypass grafting with valve replacement or aneurysm repair or both, or multiple valve replacements. Seven of the 34 Group 1 patients undergoing combined procedures had transmural myocardial infarctions compared with 2 of the 55 Group 2 patients, and 9 of the 34 Group 1 patients died cardiac-related deaths compared with 1 of the 55 in Group 2.

In comparison with Group 2, Group 1 patients demonstrated significantly more serious ventricular arrhythmias ($p < 0.01$) in the postoperative period as detected by computerized arrhythmia monitoring (Table 3). However, neither intermittent nor continuous cross-clamping affected the incidence of postoperative atrial disturbances, as the rates and severity of PAT, atrial fibrillation, and atrial flutter were similar for the two groups (Table 4). Postbypass contractility was decidedly better for Group 2, as significantly less dopamine was

*New York Heart Association Cardiac Functional Classification: Class 1—uncompromised; Class 2—slightly compromised; Class 3—moderately compromised; Class 4—severely compromised. (From New York Heart Association: Nomenclature and Criteria for Diseases of the Heart and Great Vessels. Eighth edition. Boston, Little, Brown, 1979.)

Table 2. Myocardial Necrosis Sequelae, All Cardiac Procedures

Event	Incidence (%) Group 1: Continuous Cross-clamping	Incidence (%) Group 2: Intermittent Cross-clamping	Significance
Transmural myocardial infarction	8.30 (18/217)	1.90 (5/263)	$p < 0.01$
Myocardial injury	12.40 (27/217)	5.70 (15/263)	$p < 0.02$
Cardiac death	4.60 (10/217)	0.76 (2/263)	$p < 0.02$
Need for intraaortic balloon support	4.15 (9/217)	2.66 (7/263)	NS

NS = not significant.

Table 3. Ventricular Arrhythmias, All Cardiac Procedures[a]

Arrhythmias[b]	Incidence (%) Group 1: Continuous Cross-clamping	Incidence (%) Group 2: Intermittent Cross-clamping
None	39.2 (85/217)	61.2 (161/263)
Mild	24.9 (54/217)	14.1 (37/263)
Severe	11.5 (25/217)	8.7 (23/263)
Malignant	24.4 (53/217)	16.0 (42/263)

[a] Computer tabulation for five days.
[b] $p < 0.01$ by chi-square contingency table.

Table 4. Atrial Arrhythmias, All Cardiac Procedures[a]

Arrhythmias[b]	Incidence (%) Group 1: Continous Cross-clamping	Incidence (%) Group 2: Intermittent Cross-clamping
None	70.5 (153/217)	76.4 (201/263)
Mild	16.6 (36/217)	16.0 (42/263)
Severe	12.9 (28/217)	7.6 (20/263)

[a] Computer tabulation for five days.
[b] Not significant by chi-square contingency table.

Table 5. Peak Drug Use, All Cardiac Procedures[a]

Vasopressor[b] Usage	Incidence (%) Group 1: Continuous Cross-clamping	Incidence (%) Group 2: Intermittent Cross-clamping
None	60.8 (132/217)	60.1 (158/263)
Mild	17.5 (38/217)	25.5 (67/263)
Severe	21.7 (47/217)	14.4 (38/263)

[a] Dopamine was used to keep mean pressure above either the preoperative level or 120 mm Hg systolic.
[b] $p < 0.05$ by chi-square contingency table.

utilized in that group ($p < 0.05$) than in Group 1 to keep mean postbypass blood pressures above preoperative levels or above 120 mm Hg systolic (Table 5).

Comment

Our results in a large concurrent series of patients do not support the contention that continuous aortic cross-clamping causes less clinical cardiac damage than intermittent cross-clamping during hypothermia and pharmacological cardioplegia. The theoretical increases in reperfusion edema, injury, or both in patients having intermittent aortic cross-clamping were not seen. A greater frequency of myocardial necrosis sequelae, such as transmural myocardial infarction, myocardial injury, cardiac-related deaths, and higher group mean cardiac enzymes such as SGOT and LDH, implies the converse: that the hearts subjected to intermittent aortic cross-clamping may have benefited from the brief periods of reperfusion with oxygenated blood. A statistically significant higher rate of severe ventricular arrhythmias and vasopressor usage in the group that had continous cross-clamping reinforces this concept.

It does not detract from information derived from this study that violations of protocol caused the intermittent cross-clamp group to contain a larger number of poor-risk patients who required more extensive cardiac surgery, as the resulting bias is against this group and should have worsened the results. In fact, better clinical results were obtained despite a longer cardiopulmonary bypass time and less favorable operative cases. It could be speculated that during procedures in which continuous aortic cross-clamping was employed, there might have been a tendency to hurry the operation as the anoxic period became prolonged, which could have resulted in more clinically harmful errors in this group, accounting for the poorer results. The identical mean aortic cross-clamping times for the two groups and the absence in this study of cases involving technical problems do not support this point.

Mechanisms to explain why clinical cardiac damage is not increased with intermittent cross-clamping have been extensively investigated in the laboratory. Brown and associates [3] demonstrated significant reduction of reperfusion edema during intermittent aortic cross-clamping with hypothermia alone. Wright and associates [21] showed nearly complete preservation of left ventricular function when potassium chloride cardioplegia with substrate was utilized during each aortic cross-clamping in animals subjected to intermittent anoxia. Their study also demonstrated conservation of adenosine nucleotides, especially if the hearts remained inactive during reperfusion periods. In the present study, electromechanical inactivity of the cold hearts during the brief reperfusion periods may have replicated this situation. Also, reperfusion pressures did not approach the 100 mm Hg level that is usually associated with perfusion injury [8]. Hyperosmotic or hyperoncotic cardioplegic solutions (mannitol or colloid) have been shown by Levitsky and co-workers [15] and Foglia and associates [9] to reduce myocardial reperfusion edema significantly in canine models. Our use of a hyperosmotic (348 mOsm), asanguineous coronary infusate may explain why reperfusion injury was not increased in Group 2. Perhaps the reduction in reperfusion edema allowed the reperfused blood to exert its beneficial physiological effects (replenishing substrate, providing buffer, and eluting toxic metabolites) without the deleterious effects of reperfusion edema. Indeed, the beneficial effects of so-called blood cardioplegia may be due to a modified form of intermittent aortic cross-clamping with hypothermic or pharmacological cardioplegia that negates reperfusion edema. With this technique, electrolyte-, calcium-, and pH-altered blood is perfused into the coronary circulation at 15- to 30-minute intervals under reduced pressure to interrupt the anoxic arrest periods and provide oncotic reduction of reperfusion edema, cause electromechanical quiescence of the heart, supply buffer, and replenish substrate [4, 9].

In summary, the frequency of clinical cardiac damage was not increased in a large group of patients subjected to intermittent aortic cross-clamping during anoxic cardiac arrest compared with a group that had continuous aortic cross-clamping. The utilization of hypothermia and asanguineous coronary infusates containing buffer, substrate, and potassium chloride in addition to being hyperosmotic probably reduced reperfusion edema and injury to a level that did not differ between the two groups. The better clinical cardiac performance in the group receiving intermittent aortic cross-clamping implies that hearts freed from the reperfusion injury of multiple aortic cross-clampings benefit from the salutory effects of oxygenated blood.

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Notice of Correction

In the announcement "Statement on Extracorporeal Technology" in the February issue of The Annals (Ann Thorac Surg 29:101, 1980), the last sentence should read as follows: However, it must be understood that the surgeon in charge is morally and ethically responsible for the care of the patient.

Neurogenic Respiratory Failure: A 5-Year Experience Using Implantable Phrenic Nerve Stimulators

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ABSTRACT **During the past 5 years, 20 phrenic nerve stimulators have been implanted in 11 patients who were ventilator dependent because of neurogenic respiratory failure. Ten patients had traumatic spinal cord lesions; the remaining patient suffered from a progressive demyelinating disease. There was no operative mortality. Complications included 1 stimulator malfunction and 1 pneumothorax. In spite of adjacent tracheostomies, there were no infections or wound complications. Of the 20 stimulators implanted, 13 initially produced good diaphragmatic function, 2 had fair function, and 5 had little or no function. Three patients became completely independent of their ventilators; 6 became partially independent, thus simplifying nursing care. There were no late complications. As of December, 1979, 7 patients had benefited or were continuing to benefit from phrenic nerve stimulation.**

With recent advances in cardiopulmonary resuscitation and paramedical support services, an increasing number of patients with spinal cord lesions at the first, second, or third cervical vertebra are reaching hospitals alive. Modern respiratory and general intensive care allow many of these individuals to survive their acute injuries and to become candidates for long-term rehabilitation.

Since the report by Glenn and associates [4], several centers have reported success using phrenic nerve stimulation as the sole support of ventilation in patients with high lesions of the cervical spinal cord [1, 3, 5, 6, 8, 11]. Additional experience is needed, however, to define the exact role this technique has to play in the overall rehabilitation of patients with neurogenic respiratory failure. This report analyzes the 5-year experience with implantable phrenic nerve stimulators at one regional spinal cord injury center (Northern California Spinal Cord Injury Service, Santa Clara Valley Medical Center).

Materials and Methods

Between October, 1974, and December, 1979, 11 patients with neurogenic respiratory failure were treated by implantation of phrenic nerve stimulators.* All patients were ventilator dependent at the time of operation. There were 7 male and 4 female patients, ranging in age from 6 to 52 years (mean, 25.5 years). Ten patients had sustained traumatic injury to the cervical spinal cord (from motor vehicle accidents in 6, and in 1 each from a fall, gunshot wound, stabbing, and trampoline accident). The remaining patient suffered from a poorly characterized, progressive demyelinating disease. Two patients had unilateral implantations: 1 had already received a stimulator before being transferred to our institution; the other (with demyelinating disease) had electromyographic activity on one side only. Thus, 20 stimulators were implanted in 11 patients.

Patients were not considered for phrenic nerve stimulation as long as there was any apparent improvement in their neurological function; that is, until their deficits were clinically stable. Comatose patients with no potential for meaningful rehabilitation were also excluded. All patients were tested preoperatively to show that phrenic nerve stimulation (transcutaneous or intravenous) could produce diaphragmatic contraction.

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Eight of the 10 trauma patients were apneic from the time of injury. In these patients the interval between injury and implantation of phrenic nerve stimulators ranged from 2 to 10 months (mean, 4.3 months). The other 2 patients developed slowly ascending spinal cord lesions, 1 of which did not produce respiratory failure for 15 years; phrenic nerve stimulators were implanted in these patients 4 and 15 years after injury, respectively.

The technique of stimulator insertion was that described by Glenn and associates [2, 3, 5] except that bilateral implantations were routinely performed at the same operation. Pacing was not attempted until at least 2 weeks after operation in order to allow time for healing and subsidence of perineural edema. Stimulators were then activated for 5 minutes on each side three or four times per day. Thereafter pacing was gradually extended in both duration and frequency so that after 1 or 2 months each side could be stimulated for at least 4 hours at a time. In general, unilateral stimulation was not continued more than 12 consecutive hours for fear of inducing diaphragm fatigue.

Results

There was no mortality or major morbidity associated with stimulator implantation. In spite of adjacent tracheostomies, no infections or wound complications occurred. One patient required a chest tube because of apparent transgression of the apical pleura at the time of operation.

Early Stimulator Function

Two units produced no evidence of diaphragmatic activity and were reexplored (at 3 and 6 weeks, respectively) to assure proper electrode placement; 1 of these was removed because no phrenic nerve activity could be demonstrated intraoperatively. Five units functioned only intermittently during the initial period of diaphragmatic conditioning. Most were managed by temporarily decreasing the duration and frequency of use. One electrode was reexplored and repositioned, unsuccessfully.

Thirteen of the 20 stimulators functioned well so that after 2 to 3 months the patient could be taken off all other ventilatory support for at least 4 consecutive hours. The remaining 7 units, those that had early problems, had inadequate long-term results. Two units produced small diaphragmatic contractions but inadequate tidal volumes (less than 100 cc per breath). Five stimulators failed to provide appreciable function. In all cases, ventilation was better in the supine than in the sitting position; but with active or passive abdominal support, patients could be trained to use their stimulators while sitting.

During their initial hospitalization 3 patients became completely independent of other ventilatory support; 2 of these had their tracheostomy tubes removed. Six patients were able to tolerate several hours of phrenic nerve stimulation but were returned to positive-pressure ventilation for at least part of the day.

Current Stimulator Function and Clinical Status

The status of all patients was reviewed as of December, 1979. The interval since operation was 3 to 62 months (mean, 31.5 months) for the entire group and 3 to 60 months (mean, 30.5 months) for the 8 patients who had at least 1 successful stimulator implantation.

Five patients continued to derive benefit from phrenic nerve pacing. Two of these used no other form of respiratory support; 2 others were capable of complete independence but used ventilators at night to "rest" the phrenic nerves; and 1 had only unilateral stimulator function, which he used for 12 consecutive hours each day.

Two patients had regained sufficient neurological function to breathe without phrenic nerve stimulation or other assistance. The first, a 21-year-old man who had sustained a C1-2 fracture in a motor vehicle accident in 1974, apparently had an incomplete cord lesion and was gradually weaned off phrenic nerve stimulation. The second, a 30-year-old woman with a poorly characterized demyelinating disease, had undergone unilateral stimulator insertion 1 year previously. Initially she was managed by alternating phrenic nerve stimulation with positive-pressure ventilation. As her overall neurological function gradually improved, she was weaned from the ventilator but for several weeks remained dependent upon part-time phrenic nerve stimulation. For 8 months she had been able to breathe satisfactorily without any mechanical or electrical assistance.

Three patients failed to derive any benefit from phrenic nerve pacing. One recently succumbed to a trachea–innominate artery fistula—the only death in the series. The reasons for failure in these patients are not clear but are most likely related to inadequate anterior horn cells at the C3-5 level.

The final patient had been operated upon 1 year before. At one point phrenic nerve stimulation was satisfactory for periods of 4 consecutive hours on each side; but because of gradual deterioration of his overall condition, the patient had been returned to full-time mechanical ventilation.

In summary, 7 of the 11 patients had benefited or continued to benefit from phrenic nerve stimulation. Their stimulators had been in use for 3 to 60 months (mean, 33.1 months). No late complications occurred in these patients, and there was no tendency for pacing thresholds to increase over time.

Comment

If phrenic nerve stimulation is to play an important role in the rehabilitation of patients with neurogenic respiratory failure, it will be necessary to define the criteria by which patients are selected for this mode of therapy. Menter [9] has reported 5 patients who he believes represent inappropriate use of electrophrenic pacing. Three patients had adequate vital capacities (greater than 1,000 cc) before stimulator implantation and subsequently required no long-term ventilatory support. He recommends that the decision to institute phrenic nerve stimulation be made only at a spinal cord injury center with adequate experience in the respiratory management of patients with high-level quadriplegia. (The 5 patients whom he describes received their stimulators at outlying hospitals.)

Our criteria for phrenic nerve stimulation include: (1) a high cervical lesion, (2) ventilator dependency, (3) neurological stability, (4) a functional phrenic nerve (or nerves), and (5) the potential for rehabilitation. The patient's need for long-term ventilatory assistance should be clearly established, with a low vital capacity (usually less than 100 cc), inadequate arterial blood gases, and no evidence of improvement after 2 to 3 months. Even with these criteria, 2 of our patients eventually became independent of their stimulators. It is impossible to know whether or not phrenic nerve stimulation aided their eventual recovery, but it may have done so by preventing atrophy of the diaphragm while their intrinsic neuropathy was resolving.

Given present technology, diaphragmatic pacing requires an intact phrenic nerve; that is, it is applicable only in cases of upper motor neuron dysfunction. It is therefore necessary to demonstrate integrity of the lower motor neurons of C3, C4, and C5 prior to implantation of a permanent stimulator. This can be done by delivering a transcutaneous or intravenous stimulus to each phrenic nerve and observing the diaphragm for appropriate contraction. Although in experimental animals the diaphragm can be paced, at least temporarily, by direct implantation of electrodes into the muscle after peripheral injury to the phrenic nerve, no such system is currently available for clinical use in patients with lower motor neuron lesions [7].

Glenn and colleagues [2] state that total dependency on phrenic nerve stimulation requires bilateral nerve function so that each side can be rested every few hours to prevent fatigue. In dogs, the site of fatigue has been localized to the neuromuscular junction and involves a gradual decrease of motor end-plate potentials [10]. The onset of fatigue is inversely related to duration of the pulse train and intensity of the current and is directly related to pulse interval. These studies notwithstanding, 1 of our patients tolerated several months of continuous unilateral pacing without evidence of diaphragm fatigue. As a rule, however, we prefer to limit unilateral stimulation to periods of 12 hours or less.

The complications we encountered using phrenic nerve stimulation included intermittent malfunction in 5 patients, nonfunction in 2, pain with high current in 2, and pneumothorax in 1. There have been no deaths related to operative insertion or subsequent function or malfunction of the stimulators. Although infection has not occurred in our series, it has been reported by others and mandates removal of all prosthetic material [5, 8, 9].

Others have suggested that chest wall instability [8] or chronic lung disease [9] may be contraindications to phrenic nerve stimulation. This has not been our experience. If retained secretions and atelectasis are a continuing problem, the patient who is otherwise doing well on phrenic nerve stimulation can be managed by maintaining the tracheostomy or inserting a Kirshner button to permit periodic endotracheal suctioning with or without positive-pressure ventilation.

Phrenic nerve stimulation is not designed to supplant tracheostomy and positive-pressure ventilation in the early management of patients with posttraumatic neurogenic respiratory failure. The unusually severe physiological demands made by pulmonary contusion, retained secretions, pneumonia, atelectasis, segmental or lobar collapse, and occasional fluid overload are best managed by conventional techniques. Moreover, as discussed, time is necessary to ascertain both rehabilitation potential and the need for long-term ventilatory assistance. Also, an increased incidence of infection would be expected if permanent prosthetic devices were implanted in the period immediately following injury. Even if phrenic nerve stimulators were placed at the time of initial resuscitation, several days would be needed to permit healing before stimulation was begun, and then several additional days or weeks would most likely be required to achieve optimal vital capacities. Clearly, other means of support are needed at the outset and should be continued for a minimum of 2 to 3 months before embarking upon attempts at phrenic nerve stimulation.

Our experience with phrenic nerve stimulation, based on follow-up of 3 to 62 months (mean, 31.5) as of December, 1979, includes 5 patients with continuing benefit, 2 who had former benefit, and 4 who showed no benefit. Although only 3 patients use their stimulators 24 hours a day, we believe that the others with functional units benefit from even part-time support. Nursing care is simplified, mobility is enhanced, and normal speech is possible. If the tracheostomy stoma is plugged, the upper respiratory passages are available for normal warming, humidification, and cleansing of inspired air. Moreover, phrenic nerve stimulation permits ventilation to occur by means of negative intrapleural pressure. This mechanism is more physiological than positive-pressure ventilation and may have long-term advantages which are yet to be defined.

In summary, we think complete ventilator independence should not be the only criterion of success for chronic phrenic nerve stimulation in quadriplegic patients. Based on our experience to date, we believe that phrenic nerve stimulators used in carefully selected patients with neurogenic respiratory failure are safe, reliable, potentially beneficial, and deserving of further clinical trials.

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Evaluation of Bupivacaine Nerve Blocks in the Modification of Pain and Pulmonary Function Changes after Thoracotomy

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ABSTRACT **Thirty-one patients undergoing thoracotomy were prospectively randomized to receive (1) no nerve blocks (n = 12), (2) placement of percutaneous catheters for intermittent nerve blocks with bupivacaine (Marcaine) (n = 10), or (3) bupivacaine nerve blocks intraoperatively (n = 8). One patient refused postoperative evaluation and was not included in this study. All patients received similar preoperative, intraoperative, and postoperative medications. Comparison of preoperative and postoperative arterial blood gases, assessments of pain and alertness, and chest roentgenograms showed no statistical advantage for any group. Analgesic requirements and pulmonary functions (functional residual capacity, tidal volume, minute ventilation peak flow, or forced expiratory volume) did not differ among the groups. Statistically significant differences were seen in mean respiratory rate and forced vital capacity. These differences, however, indicate that bupivacaine either by intraoperative use or by intermittent percutaneous administration did not improve postoperative increases in respiratory rate or decreases in forced vital capacity.**

Previous reports have differed widely in their conclusions as to the ability of intercostal nerve blocks to prevent postoperative pain and limit pulmonary function changes [2–6, 9, 11]. The limited systemic effect of such blocks makes this method of analgesia an attractive alternative to the opiate analgesics. Opiates may have undesirable side-effects such as sedation, nausea, vomiting, decrease in cough frequency, or hypotension.

Bupivacaine (Marcaine) is a long-acting local anesthetic, which stabilizes the neuronal membranes and prevents initiation and transmission of nerve impulses, thereby effecting local anesthetic action. Bupivacaine, when used in proper doses, offers a clear-cut advantage in duration of anesthesia. Of patients reported by Moore and colleagues [8], 67.7% experienced relief from pain 10 to 14 hours following bupivacaine administration compared with 10.5%, 11.8%, and 4.2% of patients receiving tetracaine, mepivacaine, or lidocaine, respectively. Intermittent doses of bupivacaine (epidural anesthesia) have been shown to be effective for protracted relief from pain [8]. Nerve block anesthesia utilizing bupivacaine is relatively safe; however, complications such as total spinal anesthesia, shock, allergic reactions, and systemic toxicity do exist [1, 8, 10].

The use of paracostal nerve blocks after thoracotomy has been claimed to give objective relief from pain or improvement of pulmonary function or both [2–6, 9, 11]. Placement of small polyethylene tubes in the intercostal neurovascular sheath would allow prolonged intermittent administration of local anesthetic agents and should allow a more pain-free recovery.

Materials and Methods

Thirty-one patients undergoing anterolateral thoracotomy with limited lung resection (wedge excision or lobectomy) at the National Institutes of Health were randomized at the time of operation into three groups. Group 1 (n = 12) received no nerve blocks. Group 2 (n = 10) had placement of percutaneous catheters in

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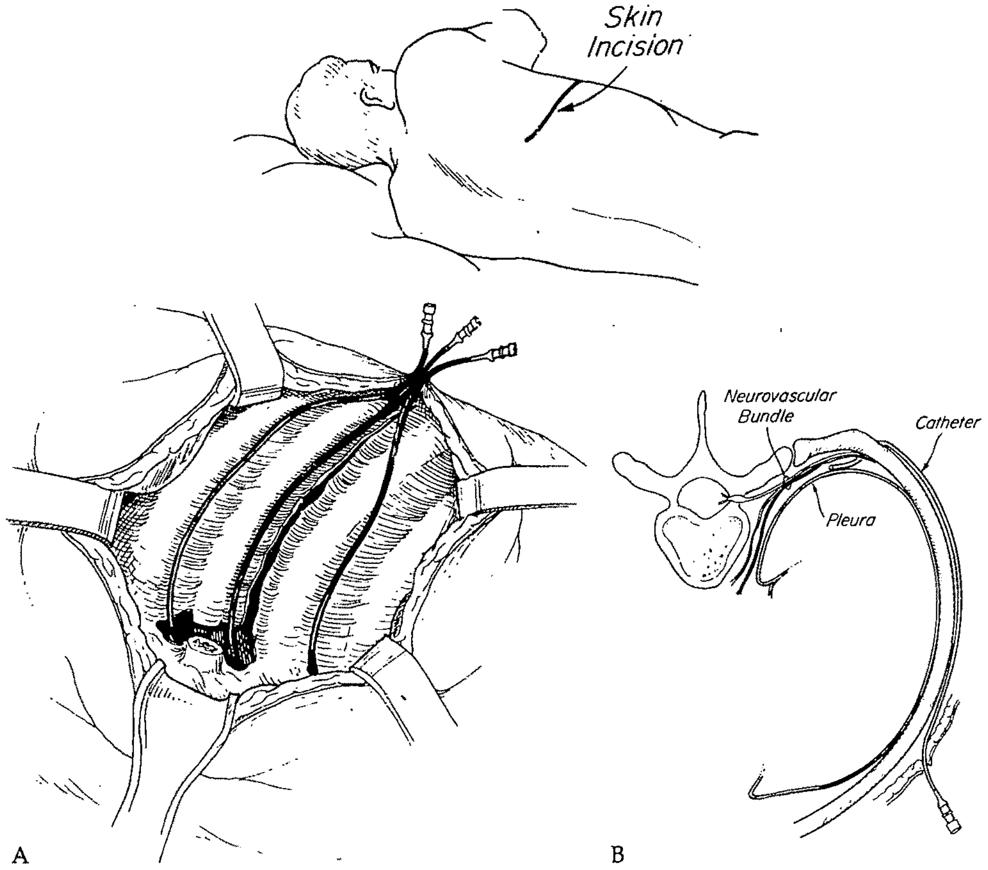

Fig 1. (A and B) Method of placement of percutaneous catheters for administration of intermittent bupivacaine intercostal nerve blocks.

three interspaces around the incision. Five milliliters of 0.5% bupivacaine was placed into each catheter intraoperatively and every 6 hours for 3 days postoperatively (Fig 1). Group 3 (n = 8) received only intraoperative nerve blocks with 5 ml of 0.5% bupivacaine in each of the three interspaces around the incision. One patient, a 12-year-old girl, was not included in this analysis because her family refused to participate in the postoperative evaluation, after randomization. All groups received atropine, 0.4 mg, and hydroxyzine, 1.5 mg per kilogram of body weight, preoperatively, no narcotics intraoperatively, and morphine sulfate on a per-weight basis every 2 hours as needed postoperatively.

Patients were excluded from this study for the following reasons: they were less than 12 years old or older than 65 years; they had a history of drug abuse or dependence; they had a history of allergy to local anesthetic agents; or they had impaired hepatic or renal function (bilirubin greater than 1.5 mg/100 ml; creatinine greater than 1.5 mg/100 ml; blood urea nitrogen greater than 20 mg/100 ml).

Preoperative evaluation included chest roentgenograms, pulmonary function testing, arterial blood gases, and patient pain assessment. Pulmonary function testing included rate, tidal volume, minute ventilation, peak flow, forced expiratory volume, forced vital capacity, and functional residual capacity. Patient pain assessments were done using 100 mm scales on which the patient was asked to mark his ability to tolerate any pain (general) and the pain of a toothache, headache, and stomachache (Fig 2). The patients were also evaluated preoperatively by a modification of the Melzack-McGill pain questionnaire [7].

Intraoperatively, if the patient had met the criteria of limited pulmonary resection (single or multiple wedge excisions of nodules, or lobectomy), a numbered card (generated by a random numbers table) directed the operating

1. Rate Your General Ability to Tolerate Pain:

I can't tolerate pain at all.	I am able to tolerate an extreme amount of pain.

2. Rate Your Ability to Tolerate the Pain of a Toothache:

I can't tolerate the pain of a toothache.	I am able to tolerate an extremely painful toothache.

3. Rate Your Ability to Tolerate the Pain of a Headache:

I can't tolerate the pain of a headache.	I am able to tolerate an extremely painful headache.

4. Rate Your Ability to Tolerate the Pain of a Stomachache:

I can't tolerate the pain of a stomachache.	I am able to tolerate an extremely painful stomachache.

Fig 2. Scales used for assessment of preoperative pain tolerance. All scales are 100 mm long.

1. How *alert* I feel:

I feel sleepy, quite unresponsive.	I feel quite alert and responsive.

2. How much *pain* I feel:

I feel quite comfortable, no apparent pain.	I am in extreme pain.

Fig 3. Scales used for patient assessment of postoperative pain and alertness. All scales are 100 mm long.

surgeon (M. W. F.) to do one of three things: (1) perform no nerve blocks; (2) place polyethylene catheters in the posterior paracostal neurovascular sheath in the interspace opened and in the interspace above and below the incision, through which 5 ml of 0.5% bupivacaine was placed at the termination of anesthesia and every 6 hours for 3 days postoperatively; or (3) perform intraoperative nerve blocks with 5 ml of 0.5% bupivacaine in the interspace opened as well as the interspace above and below.

At 2, 24, 48, and 72 hours postoperatively, patients were evaluated by the same criteria as preoperatively. Arterial blood gases were drawn 24 hours postoperatively. All patients received morphine sulfate, 0.04 or 0.08 mg per kilogram, intravenously every 2 hours as needed for pain. Pain medication was supplied only on patient request, and the nursing staff was instructed not to suggest or offer analgesics at any time. All patients initially received 0.04 mg per kilogram of morphine sulfate but could, at their request, increase the dose to 0.08 mg per kilogram if the lower dose did not provide adequate pain control. No other hypnotics, sedatives, or pain medications were allowed.

Chest roentgenograms were evaluated blindly at the termination of this study by a radiologist (A. D.), and were rated on the presence of ipsilateral or contralateral pulmonary atelectasis or consolidation and by the percent change (from preoperative) in the apical-diaphragmatic distance in an inspiratory roentgenogram. Pulmonary function tests preoperatively and postoperatively were obtained using a portable electronic spirometer, and results were expressed as the change from preoperative values for each category. Arterial blood gases obtained postoperatively were compared with preoperative measurements, and values were expressed as the change from preoperative values.

Pain and alertness assessments postoperatively were performed using a 100 mm scale (Fig 3). For each patient, preoperative pain tolerance was computed and postoperative pain assessment value (in millimeters) was subtracted from the preoperative pain tolerance value to arrive at a value we considered representative of the patient's pain, adjusted for tolerance. Observer ratings of pain and alertness were done on similar scales by the respiratory therapist (S. H.) performing the pulmonary function tests. Regional anesthesia was evaluated daily by pinpricks about the wound and along the chest wall anteriorly, laterally, and posteriorly.

In evaluating pain and changes in chest roentgenogram, pulmonary function tests, and arterial blood gases, each patient served as his own control, i.e., postoperative values were compared with preoperative values. Group means for these evaluations except pain were based on the average of the group's individual values. All statistics were performed using the Student *t* test.

Results

Comparisons of preoperative and postoperative arterial blood gases, chest roentgenograms, and pain assessments showed no statistical advantage for any group. Arterial blood gases obtained 24 hours postoperatively showed a mean decrease in partial pressure of arterial oxygen (PaO_2) of 22.2, 13.0, and 9.3 mm Hg and a change in partial pressure of arterial carbon dioxide ($PaCO_2$) of −4.1, + 1.0, and +2.8 mm Hg in Groups 1, 2, and 3, respectively. There was no statistical difference among the groups when comparing preoperative and postoperative changes in PaO_2, $PaCO_2$, or pH. Chest roentgenograms showed a mean maximal apical/diaphragmatic diameter decrease of 10.4%, 14.0%, and 16.3% in Groups 1, 2, and 3, respectively. These values, as well as the incidence of ipsilateral or contralateral atelectasis, did not differ statistically.

Patients in Group 1 experienced a mild degree of hypoesthesia immediately around the surgical wound for all 3 days. Group 2 patients were anesthetic to pinprick in the three interspaces blocked. This anesthesia gradually decreased to hypoesthesia of an area one more interspace above and below the incision, and these changes persisted for up to 24 hours after the last injected dose of bupivacaine.

Group 3 patients had a similar distribution of anesthesia, but it markedly diminished by 24 hours postoperatively. There were no paresthesias in the operative site in the three-to-six-month follow-up period of these patients to indicate long-term nerve inflammation or damage.

Table 2. Morphine Sulfate Usage

Group	Morphine Sulfate (mg/day)[a] Day 1	Day 2	Day 3
1	26.3 (0.45)	17.7 (0.30)	14.2 (0.24)
2	31.6 (0.45)	22.0 (0.31)	25.4 (0.36)
3	23.9 (0.30)	25.8 (0.32)	12.9 (0.16)

[a] Values in parenthesis are usage in milligrams per kilogram of body weight per day.

Postoperatively, there were no differences, on any day, in any group, in the absolute amount of pain experienced or in the patients' perception of alertness (Table 1). When correction for preoperative pain tolerance was done, there again was no difference among the groups on any of the 3 postoperative days. There were also no statistical differences in observed ratings of pain and alertness on any day. Although it could not be documented objectively, during the first few hours postoperatively, patients receiving intraoperative bupivacaine by either approach subjectively appeared to have less pain. This was not supported by analgesic usage or pulmonary function data.

The amount of morphine sulfate used by these patients daily or cumulatively shows no advantage for nerve block anesthesia. When comparing absolute amount of morphine sulfate used in each group or the amount of morphine sulfate used per kilogram of patient weight per day, there is no statistical difference between any two groups on any day (Table 2).

Pulmonary function changes in the postoperative period are greatest for those tests that are effort dependent. In our series there were

Table 1. Patient Rating of Postoperative Pain and Alertness[a]

	Alertness			Pain		
Group[b]	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
1	43.4 ± 22	63.8 ± 20	79.6 ± 27	57.9 ± 22	54.8 ± 22	44.0 ± 21
2	40.0 ± 22	61.7 ± 36	70.8 ± 25	71.3 ± 29	49.4 ± 27	43.8 ± 25
3	53.7 ± 24	72.1 ± 28	70.2 ± 20	53.7 ± 26	35.7 ± 36	38.0 ± 30

[a] Values shown are in mm ± standard deviation and are derived from 100 mm rating scales shown in Figure 2.
[b] Group 1, no block; Group 2, block by catheter; Group 3, single bupivacaine injection.

Table 3. Change in Respiratory Rate from Preoperative Value

	Respiratory Rate (breaths/min)		
Group	Day 1	Day 2	Day 3
1	+4.3[a]	+2.9[b]	+3.5[b]
2	+13.4[a,c]	+7.9[b]	+7.75[b]
3	+6.2[c]	+5.5	+3.65

[a] $p < 0.005$.
[b] $p < 0.03$.
[c] $p = 0.05$.

Table 4. Change in Forced Vital Capacity from Preoperative Values

	Forced Vital Capacity (cc)		
Group	Day 1	Day 2	Day 3
1	−1,513[a]	−1,251[b]	−1,028[c,d]
2	−2,140	−1,819	−2,005[d]
3	−2,420[a]	−2,242[b]	−2,110[c]

[a] $p < 0.003$.
[b] $p < 0.003$.
[c] $p < 0.005$.
[d] $p < 0.01$.

no statistical differences in the change from preoperative values in any group, on any day in tidal volume, minute ventilation, peak flow, forced expiratory volume, or functional residual capacity, an effort-independent variable. Increases in respiratory rate were seen in all groups postoperatively (Table 3). However, the greatest increases over preoperative values were seen in Group 2 (mean increase of 13.4, 7.9, and 7.75 breaths per minute on days 1, 2, and 3, respectively). This was a significant increase over the change in the control group (4.3, 2.9, and 3.5 breaths per minute on days 1, 2, and 3, respectively) ($p < 0.005$, < 0.03, and < 0.05, respectively). In addition, Group 2 and Group 3 were significantly different on day 1 ($p = 0.05$). There was also a significantly greater decrease in forced vital capacity on days 1, 2, and 3 in Group 3 (intraoperative injections), i.e., a decrease of 2,420, 2,242, and 2,110 cc on days 1, 2, and 3, respectively ($p < 0.003$, < 0.003, and < 0.005, respectively) (Table 4). The difference on day 3 between the control group and Group 2 (intermittent block by catheter) (mean decrease, 2,005 cc) was also statistically significant ($p < 0.01$).

Comment

Effort-dependent pulmonary functions such as tidal volume, inspiratory force capacity, minute ventilation, vital capacity, and forced expiratory volume when utilized in conjunction with objective assessment of local anesthesia, subjective ratings of pain and alertness, changes in arterial blood gases, analgesic usage, and the development of roentgenographic evidence of atelectasis should reflect a patient's postoperative pain and alertness accurately. Other investigators have showed changes in vital capacity [2, 4, 6, 11], analgesic usage [3, 6, 9, 11], PaO_2 [6], $PaCO_2$ [2, 6], and forced expiratory flow [6], or in subjective relief from pain [4–6, 9, 11], when intercostal nerve blocks were utilized. In some studies, patients had subcostal or flank incisions [5, 9] and thus are not directly comparable to this series. Other series were either not randomized or did not attempt to define analgesic usage by patient weight or to control for variance in dosage or frequency [2–5, 9, 11]. Toledo-Pereyra and DeMeester [11] demonstrated significant improvements in forced expiratory volume and forced vital capacity, as well as a decrease in analgesic requirement and subjective pain. These improvements lasted for approximately 7 days, far longer than would have been expected from the usual activity of bupivacaine. Kaplan and colleagues [6], in a well-defined, randomized, controlled series of 18 patients, compared the use of bupivacaine and saline solution, bupivacaine and low molecular weight dextran, and saline solution and dextran as nerve blocks. They showed significantly less decrease in PaO_2, less carbon dioxide retention, and less decrease in forced vital capacity, forced expiratory flow, and analgesic requirements for both groups using bupivacaine than for the saline solution and dextran nerve block.

In contrast, in a study of 138 patients undergoing anterolateral or posterolateral thoracotomy, Galway and co-workers [4] could find no statistically significant differences in patients' subjective relief from pain, changes in pulmonary functions, arterial blood gases, or analgesic usage when nerve blocks were utilized. As we found in the present study, they noted some beneficial effects of nerve block anesthesia in the subjective relief from pain in the initial recovery period (sixty minutes) [4].

The adequacy of the chest wall block in our study appeared to be confirmed by a transient subjective sensation of diminished pain in the area of the incision upon injection of bupivacaine by catheter and the objective anesthesia to pinprick of the chest wall surrounding the incision, in the Group 2 patients. Two of the previous groups who reported an improvement in postoperative pain also blocked three intercostal nerves [5, 9]. Of the four studies in which five interspaces were blocked, postoperative pain was diminished in three [2, 3, 11] but was not statistically influenced in the study of Galway and associates [4].

In order to adequately control for subjective pain experiences and preoperative patient differences, each patient in this series served as his own control for pulmonary function testing, chest roentgenograms, arterial blood gases, and subjective pain tolerance and assessment ratings. The entry criterion was limited to those patients undergoing limited pulmonary resection, and the patients were given medications in a similar manner. In an effort to define a possible prolonged effect of bupivacaine intercostal nerve blocks, the intermittent percutaneous administration of bupivacaine for 3 days, as well as a single injection was studied. In this series we have seen no improvement in analgesic usage, arterial blood gases, pulmonary function testing, chest roentgenograms, patient's subjective rating of pain and alertness, or in observer's subjective rating of pain and alertness. Thus we were unable to define any objective short-term or long-term benefits from bupivacaine nerve block anesthesia in patients undergoing thoracotomy.

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Assessment of Prospectively Randomized Patients Receiving Propranolol Therapy before Coronary Bypass Operation

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ABSTRACT **Fifty patients receiving propranolol were randomized into two groups of 25 patients each. One group received the last dose of propranolol within 4 hours of operation and were on a regimen of 160 mg daily. The second group had propranolol discontinued 24 to 48 hours prior to operation. Two nonrandomized control groups consisted of 25 patients who had never had propranolol and 15 patients who were on a regimen of 160 mg or more and who were operated on for unstable angina. Blood levels of propranolol were obtained just prior to incision.**

Several hemodynamic variables were assessed prior to anesthetic induction, at peak response during the early anesthetic period, and at the termination of cardiopulmonary bypass. Strict criteria were enforced for the administration of inotropic agents and the incidence of myocardial injury in the various groups was tabulated. Significant differences were present in the form of lower pressure-rate products in the patients maintained on propranolol therapy. The incidence of inotropic support, however, was also higher within the subgroups of patients who had propranolol immediately prior to operation. When examined further, increased inotropic requirements existed in patients having 320 to 480 mg of propranolol just before operation; this finding correlated with serum propranolol levels measured at the time of operation. This tightly controlled study supports the maintenance of propranolol for its beneficial perioperative hemodynamic effects but suggests that maintenance of doses of 320 to 480 mg per day are associated with a greater duration and extent of action that may transiently affect early postoperative hemodynamic performance.

The use of propranolol as part of the immediate preoperative pharmaceutical program for patients undergoing aortocoronary bypass grafting has been controversial. Despite early warnings relating preoperative beta blockade to high operative risks, most investigators have discerned little difference in patients receiving propranolol preoperatively compared with patients in whom the medication was discontinued. As summarized in Table 1, most information has been gleaned from reports of successive cohorts of patients and only one prior investigation used a clinical study in which propranolol maintenance or withdrawal was prospectively randomized. Moreover, most comparisons were made between groups of patients maintained on propranolol to within 36 to 48 hours of operation compared with groups of patients in whom propranolol was discontinued several days in advance of the operative procedure. This study compares patients maintained on substantial doses of propranolol in the immediate preoperative period with a group of patients in whom the medication was discontinued 24 to 48 hours prior to operation.

Material and Methods

Ninety patients were included in the study. Informed consent was obtained from all patients who participated in the study, and the entire investigational protocol was approved by the Human Experimental Investigation Committee. Fifty patients receiving long-term propranolol therapy who were admitted for elective aortocoronary bypass operation were randomly assigned to one of two groups of 25 patients

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Table 1. Previous Investigators Reporting on the Use of Propranolol in the Immediate Perioperative Period

Author	Year	Type Study	Patients on Propranolol	Patients off Propranolol
Viljoen et al [14]	1972	Case reports	5	0
Caralps et al [2]	1974	Retrospective	25	75
Moran et al [10]	1974	Retrospective	52	251
Kaplan et al [7]	1975	Retrospective	143	26
Jones et al [6]	1976	Retrospective	113	72
Kirsh et al [8][a]	1978	Prospective randomized	14	13
Boudoulas et al [1]	1978	Retrospective	30	50

[a]This study represents the only other investigation in which a prospectively randomized format for propranolol management was used.

each. One group had propranolol discontinued 24 to 48 hours prior to operation. Regardless of the dose taken on admission, these patients were maintained on 160 mg of propranolol daily prior to cessation of therapy. Eighteen patients were on a regimen of 160 mg of propranolol daily and 7, 320 to 480 mg daily. The second group of 25 patients were maintained on propranolol and received the last dose 4 hours prior to operation. Patients receiving more than 160 mg of propranolol daily were reduced to 160 mg daily 24 to 48 hours prior to operation. Of this group, 16 patients were on a regimen of 160 mg daily and 9, 320 to 480 mg daily. A third group of patients, in whom therapy was not randomized, consisted of 25 successive patients admitted for elective aortocoronary bypass operation. These patients were not receiving propranolol. A fourth group consisted of 15 patients who underwent operation for unstable angina pectoris and who were receiving propranolol up to 4 hours prior to operation. These patients did not have the propranolol dosage reduced regardless of the admission dosage program.

Statistical comparisons were made only between the two groups of patients in whom drug therapy was prospectively randomized. All patients were men, and computer analysis of patient variables among the four groups was used to assess multiple descriptors by analysis of covariance to determine the comparability of the groups. This analysis included the incidence of left main coronary disease of greater than 70% obstruction, resting ejection fraction, presence or absence of mitral valve regurgitation, presence or absence of congestive heart failure, presence or absence of resting S-T segment and T wave changes, patient age, history of prior myocardial infarction, arterial venous oxygen saturation difference, number of diseased vessels, evidence of ventricular dysfunction on cineangiogram, and the presence or absence of cardiomegaly on chest roentgenogram. For these descriptors, patients operated on for unstable angina (not randomized) had a higher incidence of left main coronary artery disease, as indicated in Table 2, but were otherwise indistinguishable. In addition to the patient risk descriptors just described, the perioperative pressure–heart rate product was calculated on arrival in the operating room, at the peak response during anesthetic induction, and 30 minutes following termination of cardiopulmonary bypass. The incidence of myocardial infarction was determined from the presence of new Q waves on the postoperative electrocardiogram and a myocardial damage index was calculated for the patients having prospective randomization of their propranolol programs by determining the area under a CPK-MB duration curve level with samples being drawn at 6-hour intervals for the first 72 hours after operation. Requirements for inotropic support were recorded both for patients who required such support to terminate cardiopulmonary bypass and for patients who required initiation of such support within the first 24 hours after opera-

Table 2. Critical Variables for the Patient Groups Studied

Variable	OP	P	P̸	P(NR)
Left main coronary disease > 70% (%)	16	16	20	33[a]
Resting ejection fraction (%)	43 ± 5.2	44 ± 4.6	47 ± 5.1	41 ± 3.9
No. of grafts	2.6 ± 0.14	2.9 ± 0.19	2.8 ± 0.15	2.9 ± 0.21
Cross-clamp time (min)	36 ± 4.1	34 ± 3.7	37 ± 2.9	37 ± 4.3

[a] $p < 0.01$. This was significantly different from all the other groups.

OP = patients never receiving propranolol; P = patients receiving the last dose of propranolol 4 hours prior to operation; P̸ = patients receiving long-term propranolol therapy, discontinued 24 to 48 hours prior to operation; P(NR) = patients with unstable angina who received the last propranolol dose 4 hours prior to operation.

tion. The incidence of hypertension requiring nitroprusside therapy was noted as was documentation of arrhythmias. Propranolol serum levels were obtained in each patient at the time the skin incision was made. The Student *t* test for unpaired data was used to calculate differences between the randomized groups.

Basic Operative Techniques

A standardized method of operation was used for all patients in the study. This included anesthetic induction with diazepam (Valium) and morphine and maintenance with morphine, nitrous oxide, and pancuronium. Hemodilution techniques were employed; however, the hematocrit was not allowed to fall below 20% during the period of cardiopulmonary bypass. Systemic temperatures were maintained at 30°C and operations were performed using hyperkalemic, crystalloid cardioplegia (5°C) with a potassium concentration of 24 mEq per liter. Proximal anastomoses were performed prior to distal anastomoses and following an initial cardioplegic infusion of approximately 500 ml per square meter of body surface area. Supplements of cardioplegic solution were infused after the completion of each distal anastomosis (usually 150 to 200 ml). Left ventricular venting was not employed, and reperfusion was greater than or equal to half the aortic cross-clamp time.

Strict criteria for inotropic support were employed. Inotropic agents were used to terminate cardiopulmonary bypass when the patient was unable to maintain a blood pressure greater than 110 mg Hg systolic or when the systolic pressure was less than 20% below control levels, and when the pulmonary artery diastolic pressure, pulmonary capillary wedge pressure, or left atrial mean pressure was greater than 15 mm Hg. A decision to employ inotropic support following termination of cardiopulmonary bypass was made for a cardiac index less than 2 or when the pulmonary artery diastolic pressure, pulmonary capillary wedge pressure, or left atrial mean pressure was greater than 15 mm Hg. If isolated hypotension was present with cardiac indices greater than 2 L/min/m^2, alpha agonists were employed.

Results

Table 2 summarizes the salient intraoperative features for the four study groups. No significant differences among the groups in the number of grafts or the aortic cross-clamp times existed. Table 3 lists the principal comparisons made among the groups. In addition to these, the incidence of important arrhythmias was not different for the two groups. Significant differences between the two groups in which propranolol therapy had been randomly managed were confined to the pressure-rate product determined at all three measurement points as well as in the requirement for inotropic support, particularly within the first 24 hours. The increment in inotropic support between that required to terminate cardiopulmonary bypass and that initiated within the first 24 hours for all patients occurred within 6 hours of return to the intensive care unit. The mean propranolol serum level was also higher in the group in which propranolol had been maintained compared with the group in which it had been discontinued. These differences are examined in more detail in Figures 1, 2, and 3.

As illustrated in Figure 1, significant differences existed in the basal pressure-rate product among patients maintained on propranolol and

Table 3. Chief Variables Compared in Study

Variable	OP	P	℞	P(NR)
Arrival pressure-rate product	11,242 ± 722	6,960 ± 421[a]	11,480 ± 803	6,640 ± 501
Peak pressure-rate product	17,400 ± 902	10,800 ± 629[a]	18,100 ± 1151	11,200 ± 781
Postpump pressure-rate product	12,146 ± 513	9,422 ± 622[a]	13,114 ± 877	9,017 ± 536
Pump inotropic support	2/25	1/25	2/25	2/15
24-hr inotropic support	2/25	7/25[a]	1/25	4/15
Required nitroprusside[b]	15/25	12/25	16/25	8/15
Acute myocardial infarction[c]	1/25	1/25	0/25	1/15
Myocardial damage index > 200	2/25	3/25	1/25	2/15
Propranolol level	0	16.4[a]	3.1	20.2

[a] $p < 0.01$ when compared with randomized patients in whom propranolol was discontinued 24 to 48 hours prior to operation.

[b] Figures represent the absolute number of patients in each group requiring nitroprusside administration for control of postoperative hypertension.

[c] As defined by the appearance of new Q waves.

OP = patients never receiving propranolol; P = randomized patients receiving the last dose of propranolol 4 hours prior to operation; ℞ = randomized patients in whom propranolol was discontinued 24 to 48 hours prior to operation; P(NR) = patients with unstable angina who received the last propranolol dose 4 hours prior to operation.

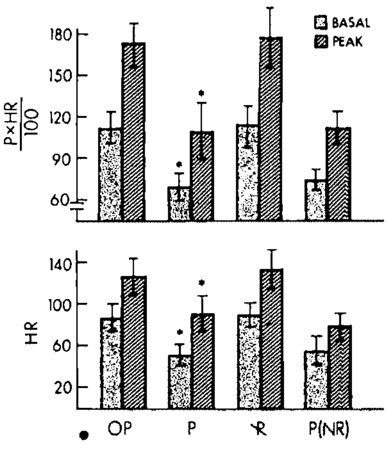

Fig 1. (Top) Pressure-rate product (P × HR) ×10^{-2} *on arrival in the operating room and at peak response during anesthetic induction for each of the four study groups. (Bottom) Heart rate* (HR) *determined at the same times as the pressure-rate product.* (OP = *patients never receiving propranolol;* P = *patients receiving the last dose of propranolol 4 hours prior to operation;* ℞ = *patients receiving long-term propranolol therapy discontinued 24 to 48 hours prior to operation;* P(NR) = *patients with unstable angina who received the last propranolol dose 4 hours prior to operation;* * = $p < 0.01$ *when compared with the randomized group in which propranolol was discontinued 24 to 48 hours prior to operation.)*

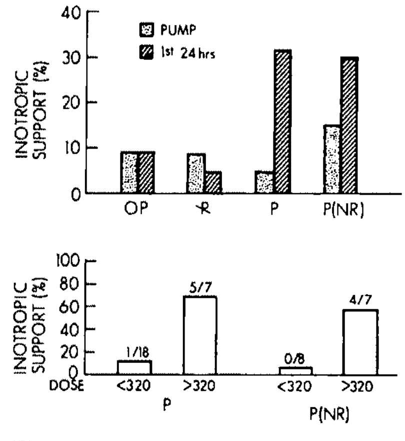

Fig 2. (Top) Percentage of patients in each of the subgroups requiring inotropic support either to terminate cardiopulmonary bypass or within the first 24 hours after cardiopulmonary bypass. There was a significant difference ($p < 0.05$) *between the two groups of patients in the randomized treatment protocol as there was between the patients maintained on propranolol who had unstable angina compared with those not receiving propranolol or in whom propranolol had been discontinued. (Bottom) Comparison of patients maintained on propranolol and having inotropic support requirements as a function of propranolol dosage.* (OP = *patients never receiving propranolol;* P = *patients receiving the last dose of propranolol 4 hours prior to operation;* ℞ = *patients who had long-term propranolol therapy discontinued 24 to 48 hours prior to operation;* P(NR) = *patients with unstable angina who received the last propranolol dose 4 hours prior to operation.)*

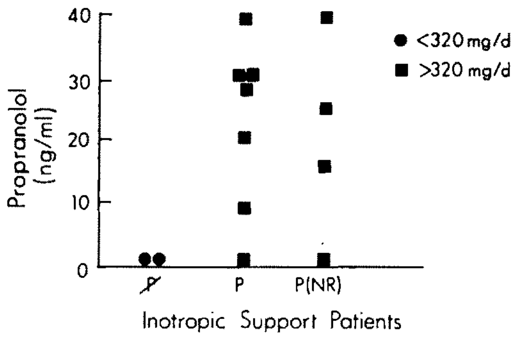

Fig 3. Relationship between serum propranolol levels and the dosage of propranolol in patients requiring inotropic support anytime within the perioperative period. (P̸ = patients who had long-term propranolol therapy discontinued 24 to 48 hours prior to operation; P = patients receiving the last dose of propranolol 4 hours prior to operation; P(NR) = patients with unstable angina who received the last propranolol dose 4 hours prior to operation.)

those in whom the drug was discontinued. Similarly, there was suppression of the elevation in pressure-rate product that accompanied induction of anesthesia in this group as well. These observations paralleled closely the comparison among nonrandomized patients not receiving propranolol compared with patients not randomized and operated on for unstable angina who were maintained on propranolol. In both the randomized and nonrandomized groups, maintenance of propranolol therapy was associated with significantly lower pressure-rate products on arrival in the operating room and during the anesthetic induction period. Separate analyses of heart rate as shown in the lower half of the figure showed parallel significant suppression of heart rate response to anesthetic induction in both propranolol-treated groups. Moreover, the heart rate differences appear primarily responsible for the decreased pressure-rate products in the group of patients maintained on propranolol therapy.

A more detailed analysis of patients requiring inotropic support is presented in Figure 2. Patients who underwent randomization of propranolol therapy with withdrawal of drug 24 to 48 hours prior to operation had an incidence of inotropic support requirement that paralleled closely the group of patients never receiving propranolol treatment. A significantly greater percentage of patients required inotropic support in the group of patients randomly maintained on propranolol, which paralleled the incidence of inotropic support in patients operated on for unstable angina who continued propranolol treatment. In the upper half of the figure, almost 30% of patients maintained on high-dose propranolol therapy required inotropic support using the criteria described in the Methods section. Further breakdown of the patient subgroups is shown in the lower portion of the figure where the percentage of inotropic support for patients receiving continued propranolol therapy is shown. An increased incidence of inotropic support was noted only in patients receiving more than 320 mg of propranolol daily and approached 60% of that population. On the other hand, patients being maintained on propranolol but in doses of less than 320 mg had an incidence of inotropic support requirement no greater than patients either not receiving propranolol or in whom propranolol was discontinued 24 to 48 hours prior to operation.

The relationship between the dosage of propranolol maintained and the serum propranolol level in the patients requiring inotropic support is illustrated in Figure 3. Only 2 patients receiving less than 320 mg per day of propranolol required inotropic support. Both these patients were in the randomized group in which propranolol had been discontinued 24 to 48 hours prior to operation, and both these patients had no detectable serum levels of propranolol. All the patients in the randomized group that had propranolol discontinued 24 to 48 hours prior to operation had no detectable serum levels of propranolol as was true for the group of patients never receiving propranolol therapy. Of the patients requiring inotropic support in the groups maintained on propranolol until the time of operation, 7 patients had 20 ng per milliliter or greater concentration of propranolol, while 4 had concentrations below that level. No propranolol levels greater than 10 ng per milliliter were found in patients in either of the groups maintained on propranolol who did not require inotropic support.

Comment

The data presented in this study generally support the notion that continuance of propranolol therapy to the time of operation is safe and potentially beneficial. The reduced pressure-rate product in patients maintained on propranolol in the absence of untoward anesthetic events appears to be a highly desirable benefit of such therapy, particularly for the suppression of the heightened pressure-rate product that generally accompanied the process of intubation in patients not receiving propranolol or in whom propranolol had been discontinued 24 to 48 hours prior to operation.

The finding of substantial levels of propranolol in the serum of patients maintained to the time of operation is not inconsistent with prior reports on the half-life of serum propranolol. Thirty-six to 48 hours following discontinuation of propranolol therapy, most investigators have shown no serum propranolol present, absent propranolol from atrial tissue excised at operation, and a normal response to pharmacological beta stimulation [2–5, 11, 12]. The propranolol levels in patients maintained on the drug to the time of operation were significantly higher than in patients in whom the drug had been discontinued. In patients requiring inotropic intervention, the daily dosage of propranolol was invariably 320 mg or more, even though reduced to 160 mg 24 to 48 hours prior to operation in the group of patients who underwent randomization of the therapeutic programs. It was interesting to note that more patients in the group requiring inotropic support evidenced their need for such support within several hours of operation than did those requiring inotropic intervention to terminate cardiopulmonary bypass. It is possible that intense levels of neurogenic and humoral catecholamine stimulation in the period immediately after pump removal allowed adequate maintenance of beta function to support systemic hemodynamics. With some withdrawal of this intense stimulation, and in the presence of significant propranolol levels or beta-blocking hepatic metabolites of propranolol (not measured in this study), a dependence on exogenous beta stimulation may have resulted. In all patients, beta agonists could be withdrawn within 24 hours of operation, perhaps suggesting the dislodgment of beta blockers and subsequent metabolic degradation of these rather than intrinsic myocardial injury and depression.

This study differs from previous investigations in several respects. It utilized a tightly controlled patient population under the care of a single surgeon. A primary comparison was possible between two groups of patients in whom propranolol therapy could be managed in a randomly allocated fashion. The issue addressed was related more to the relative safety of maintaining propranolol in significant doses immediately prior to the time of operation compared with following the more recommended protocol of discontinuing propranolol 24 to 48 hours prior to operation. Most previous investigations were concerned primarily with the question of discontinuing propranolol several days in advance of the procedure or maintaining it to within 24 to 48 hours of operation. In our population of patients studied in whom propranolol was discontinued 24 to 48 hours prior to operation, there was no evidence of a "propranolol rebound phenomenon," confirming the safety of this conservative approach to management of propranolol dosage [9, 13].

As a result of this investigation and after consideration of prior reports appearing in the literature, it appears beneficial to maintain propranolol in patients with unstable angina or those with unusually severe angina by history at outpatient levels immediately prior to the time of operation because of the desirable perioperative hemodynamic effects. The surgeon should anticipate that patients so maintained, who are receiving doses of propranolol in excess of 320 mg daily, may require inotropic support transiently in the perioperative period. But such support will be temporary and does not appear to correlate with demonstrable myocardial injury.

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Discussion

DR. ELLIS L. JONES (Atlanta, GA): I congratulate Dr. Wechsler for a very well conceived and well executed clinical study, which is so characteristic of the work from Duke. Our initial experience dates back to 1975 when my colleagues and I reviewed the records of 185 consecutive patients having myocardial revascularization. We looked at the preoperative administration of propranolol and the intraoperative or postoperative complications.

The 185 patients were arbitrarily divided into four groups. Group 1 patients had propranolol continued to within 10 hours of induction of anesthesia. In Group 2, propranolol was discontinued 24 to 48 hours before operation. In Group 3, propranolol was discontinued more than 48 hours before operation, and Group 4 patients never were administered the drug at all. For the most part, the dosages were in the low and intermediate ranges, although a few patients were at the higher levels—320 to 480 mg a day.

The incidence of complications, e.g., hypotension, bradycardia, hypertension, and tachycardia, prior to cardiopulmonary bypass was no greater in patients on a regimen of propranolol up until the time of operation than in patients who had the drug discontinued in advance or had never received the drug. It was very interesting that the incidence of hypertension and tachycardia, the factors that control rate-pressure product and myocardial oxygen consumption, was no greater and probably a little less in those patients administered propranolol the night before operation.

Postoperatively there was no greater incidence of hypertension requiring inotropic support or balloon pumping and no greater mortality in Groups 1 and 2 (recently on a regimen of propranolol) compared with those in Group 3 or 4. The time of our study was 1975, when patients on a regimen of beta-blocking drugs were routinely withdrawn from the drug seven days prior to revascularization.

We measured the serum levels of propranolol and, as Dr. Wechsler mentioned, found a difference in levels for the different groups of patients. Those on low and intermediate doses of propranolol had no significantly detectable serum levels by the end of cardiopulmonary bypass. However, for those patients given very large doses of the drug, serum levels were still present at the conclusion of the operation.

Since adopting the policy of continuing propranolol until the night prior to operation, we have found the incidence of inotropic requirement has decreased over the years, and the incidence of intraaortic balloon pumping is about 1%. Hospital mortality in our last 3,040 patients has been 0.8% (25 deaths). We, therefore, believe our present philosophy regarding propranolol has not influenced our clinical results adversely.

In conclusion, data are very scanty for patients on a regimen of extremely large doses of beta-blocking agents. Their numbers in our practice are very small. Our cardiologists appear to have gone through a transition in their thinking. If patients fail to respond to the low and intermediate doses, they are recommended for operation and are not carried to the extremes of medical management.

I have one question for Dr. Wechsler. Have you employed test doses of isoproterenol in patients who receive large doses of propranolol after bypass to see if there is residual beta blockade?

DR. CHARLES W. PEARCE (New Orleans, LA): It has been my privilege in New Orleans to do cardiac surgical procedures in three different hospitals and thus to work with three different cardiology groups. One of these groups typically uses quite large doses of propranolol in patients. It is quite common for the patients to receive doses of 320 to 480 mg of propranolol right up through the evening prior to operation. Another group tends to use propranolol in moderate dosage and the third, in quite low dosage.

During the past year we have operated on 392 consecutive patients. There has been no hospital mortality. However, those of us operating on the patients whose cardiologists typically use large doses of propranolol, 320 to 480 mg, have made these observations: prolonged pump support is often necessary before these patients can be weaned from the pump, and additional inotropic support is necessary at that point and in the early period following operation.

These observations, I think, support Dr. Wechsler's general observation that a propranolol dosage of high magnitude does indeed have some definite effect on myocardial function in the operative and the early postoperative period.

DR. RONALD M. BECKER (Pelham, NY): We have also been interested in the effect of propranolol withdrawal on perioperative hemodynamics. Some of our data were presented at the recent American Heart Association meeting in Anaheim.

We studied four groups of patients, each containing 17 to 20 patients. Group 1 never received propranolol; in Group 2, propranolol was discontinued 48 hours preoperatively; in Group 3, it was discontinued 10 hours preoperatively; and in Group 4, it was continued throughout the operation and restarted postoperatively in small intravenously administered doses.

We also looked at rate-pressure products and found no differences in the responses when propranolol was discontinued 48 hours preoperatively (Group 2) or 10 hours preoperatively (Group 3). Both groups demonstrated huge increases in rate-pressure products on induction of anesthesia. By contrast, there was a marked blunting of this effect in patients in whom propranolol was continued throughout the operation (Group 4). In addition to blunting the increases in rate-pressure product, we found that maintenance of propranolol resulted in a marked decrease in postoperative atrial arrhythmias compared with those groups in whom propranolol was discontinued.

I will remind you that a large percentage of perioperative infarctions are initiated in the prebypass phase of the operation. Maintenance of beta blockade prior to revascularization should minimize the potential for perioperative infarction.

I thank Dr. Wechsler for providing me with a copy of his manuscript. I agree that maintenance of propranolol is not only safe but is often beneficial, and we continue to use it aggressively and to reinstitute propranolol as soon as the patient returns to the intensive care unit.

I have one question for Dr. Wechsler. I noticed that his group uses morphine anesthesia. I consider this a poor choice for patients having a coronary operation since morphine does not block cortical responses to stress. Perhaps Dr. Wechsler could comment on his choice of anesthetic agent.

DR. RICHARD D. WEISEL (Toronto, Ontario, Canada): A randomized trial of intravenously administered propranolol was performed in 100 patients undergoing elective coronary bypass operation at the Toronto General Hospital under the direction of Drs. Dosch and Teasdale. In 50 control patients, propranolol was discontinued 8 hours preoperatively and in 50 patients it was continued by an infusion of 0.04 mg per kilogram of body weight per hour intraoperatively and for 36 hours postoperatively. Serum propranolol levels revealed that only control patients receiving more than 160 mg per day had measurable propranolol levels during anesthesia induction. This information supports Dr. Jones's findings. The propranolol group had a lower rate-pressure product during anesthesia induction and a lower incidence of postoperative arrhythmias. Did Dr. Wechsler also find fewer postoperative arrhythmias?

A subgroup of 20 patients randomly allocated to a group to receive intravenously administered propranolol or to a control group, had serial measurements of postoperative myocardial performance and metabolism. The propranolol group had depressed performance compared with the control group but responded to atrial pacing by lactate extraction whereas control patients produced lactate in response to atrial pacing in the immediate postoperative period (2 to 6 hours).

An infusion of propranolol perioperatively may protect the ischemic myocardium, but renders the patient very sensitive to hypervolemia or hypovolemia. Therefore, it must be used with caution.

DR. WECHSLER: I thank Dr. Jones, Dr. Pearce, Dr. Becker, and Dr. Weisel for their comments. Dr. Jones, we did not do isoproterenol testing. I think it would have been a good maneuver to look for residual physiological effects of the propranolol.

Regarding the use of morphine sulfate, the anesthesiologists at the time of the study used that method exclusively. In answer to your question, I think the trend has been to revert to inhalation anesthetics, and currently the large doses of morphine are not used.

We did not find that there was a decrease in the incidence of atrial arrhythmias in those patients in whom the propranolol had been maintained to the time of operation. Dr. Weisel, perhaps your study differs from ours in that you maintain the drug through the operative period. Dr. Becker, I can't explain why we didn't make this observation and you did.

I have a final comment. This study provides a bit of a caveat. Initially there was concern that patients could not be continued on propranolol to the immediate operative time, and most studies analyzed the effect of withdrawal of the drug several days before operation as compared with 24 to 48 hours prior to operation. There have only been one or two studies in which the drug was continued right to the time of operation in significant doses. Using doses of 320 to 480 mg, such as our high-dose patients were receiving, has not been documented before except in a few of the patients in Group 1 of Dr. Jones's study. In this subgroup of patients, there clearly are high serum levels present at the time of operation. Moreover, metabolites become present during operation as the result of hepatic detoxification. Some of these metabolites are beta blockers that do not show in serum propranolol assays but which do have a pharmacological effect. Of course, the beta block can be reversed simply by the use of beta agonists in the perioperative period if necessary.

Notice from the American Board of Thoracic Surgery

The American Board of Thoracic Surgery will give a voluntary recertification examination in the fall of 1981. Diplomates interested in participating in this examination should maintain a documented list of their cardiothoracic operations performed two years prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings and other continuing medical education activities for the two years prior to application for recertification.

Some time during the summer, a Recertification Brochure will be mailed to all diplomates outlining the rules and requirements established for recertification in thoracic surgery. This brochure will also contain information about applying for the voluntary recertification examination.

Please address all communications to the American Board of Thoracic Surgery, 14640 E Seven Mile Rd, Detroit, MI 48205.

Postoperative Angiographic Assessment of Modified Blalock-Taussig Shunts Using Expanded Polytetrafluoroethylene (Gore-Tex)

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Philip Rees, M.R.C.P., James F. N. Taylor, M.D.,
Fergus J. Macartney, M.B., and Jaroslav Stark, M.D.

ABSTRACT **Thirty-six of 87 modified Blalock-Taussig shunts done with expanded polytetrafluoroethylene (Gore-Tex) were restudied angiocardiographically. In 7 patients the study was carried out within 1 month of the shunt operation because the patients failed to make satisfactory clinical progress. Two shunts were occluded and 1 was stenosed; all 3 were in neonates. The remaining 29 patients were reinvestigated electively between 5 and 29 months postoperatively and had a 97% shunt patency rate. Because of the rather high incidence of irregular or stenosed shunts among neonates with 4 mm conduits, we now prefer to use a larger conduit even in this age group.**

A subclavian–pulmonary artery shunt constructed on the side opposite the aortic arch offers the best palliation among the various systemic–pulmonary artery shunts. However, when the anatomy is considered unsuitable for direct anastomosis between the subclavian and pulmonary arteries, classic shunt operations have been accomplished only with a substantial risk of failure [9, 12] or later development of pulmonary vascular disease [16] and distortion of the pulmonary arteries [17, 19]. Since April, 1975, we have been using the modified Blalock-Taussig anastomosis described here when the classic shunt was unsuitable. A prosthesis with a diameter greater than that of the subclavian artery is sutured end-to-side to the undivided subclavian artery and to the pulmonary artery. Thus, blood flow through the shunt is initially limited by the diameter of the subclavian artery, and there should be a potential for flow to increase with growth. In order to assess the validity of these concepts, we have reviewed the postoperative angiocardiograms performed in some of these patients.

Clinical Material

Prostheses of woven Dacron were used in 13 patients in the early part of our experience. Since October, 1976, we have utilized prostheses of expanded polytetrafluoroethylene (PTFE) (Gore-Tex), and by the end of December, 1979, we had carried out 87 modified Blalock-Taussig anastomoses with this material.

The operation may be performed on either side through a lateral thoracotomy in the fourth intercostal space. The pulmonary artery is dissected as for the classic Blalock-Taussig shunt. A side-biting clamp is placed on the origin of the dissected subclavian artery, and the obliquely trimmed prosthesis is anastomosed end-to-side on the subclavian artery with continuous Prolene. Heparin, 1 mg per kilogram of body weight, is given intravenously before the Gore-Tex conduit is anastomosed to a transverse arteriotomy made on the anterior aspect of the pulmonary artery near its upper edge.

Thirty-six shunts (41.4%) have now been investigated with selective angiocardiography. In 7 cases, cardiac catheterization was carried out within 1 month of the shunt operation because the patients failed to make satisfactory clinical progress. The remaining patients were reinvestigated electively between 5 and 29 months (mean, 15.6 ± 5.5) postoperatively. These are more representative of the group of patients being studied. Biplane cineangiocardiograms were reviewed for shunt patency, irregularities of the inner surfaces of the prosthesis, distor-

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tion of pulmonary arteries, and anastomotic stenosis. Enlargement of the pulmonary arteries following systemic-pulmonary anastomosis was calculated in 9 patients by measuring the diameter of the main right and left pulmonary arteries just proximal to their lobar branching and comparing the diameter with that of the descending thoracic aorta at the level of the diaphragm [7]. Measurements were made on the same frame of the angiogram or, when this was not possible, on frames taken at the same part of the cardiac cycle. All data are given as mean ± 1 standard deviation; the significance of difference was estimated by unpaired t test. Because 1 Dacron shunt occluded shortly after direct cannulation at cardiac catheterization, it has been assumed that the neointima could be dislodged from the Gore-Tex prosthesis as well. For this reason, catheters were not passed through the shunt for pressure measurements or injection of contrast medium.

Results

Early Reinvestigation

Among the 7 patients reinvestigated early (Table 1), the shunt was occluded in 2 and stenosed in 1. The first occlusion occurred in an infant with pulmonary atresia and intact ventricular septum who at the age of 1 day underwent transpulmonary valvulotomy and left shunt using a 4 mm Gore-Tex prosthesis. On the first postoperative day the shunt murmur had disappeared and a fall in oxygen tension was noted. She was subsequently maintained by prostaglandin infusion. Postoperative angiography demonstrated occlusion at the subclavian anastomosis. The patient underwent reoperation at the age of 8 days. The shunt was found to be occluded on the subclavian end but was still patent distally. The anastomosis was successfully reconstructed, and the patient was well 11 months postoperatively.

The second patient had a univentricular heart with left atrioventricular valve atresia and pulmonary stenosis, and was operated on at the age of 3 weeks while in low cardiac output. His condition was fair postoperatively but a shunt murmur could not be heard. On this basis he was reexplored on the same day. The shunt was incised transversely and found to be patent; the incision was closed by direct suture. The following day the patient was still in low cardiac output, and an angiocardiogram was performed. The shunt was now occluded by a thrombus, which at postmortem examination was seen to originate at the level of the incision made in it at reexploration (Fig 1).

The stenosis occurred in an infant with tricuspid atresia who had a shunt performed at the age of 9 days. Increasing cyanosis was noted three weeks postoperatively, and angiocardiograms revealed anastomotic stenosis at the subclavian end. A left modified Blalock-Taussig anastomosis was performed successfully, and the patient was well 17 months postoperatively.

Elective Reinvestigation

The 29 patients who underwent elective reinvestigation have been followed in outpatient clinics for 12 to 38 months postoperatively (mean, 25.7 ± 7.1). The diagnoses are summarized in Table 2. All initially improved in

Table 1. Findings at Early Reinvestigation of 7 Patients with Modified Blalock-Taussig Shunts (Gore-Tex)

Diagnosis	Age	Weight (kg)	Status of Shunt	Outcome
Pulmonary atresia + VSD	12 days	2.2	Patent	Died
Pulmonary atresia + IVS	1 day	3.6	Occluded	Reoperated
Univentricular heart + PS	3 wk	3.8	Occluded	Died
Tricuspid atresia + PS	4 mo	3.3	Patent	Died
Pulmonary atresia + VSD	19 days	3.8	Patent	Died
Tricuspid atresia + PS	9 days	2.0	Stenosed	Reoperated
Pulmonary atresia + VSD	5 yr	19.0	Patent	Improved

VSD = ventricular septal defect; IVS = intact ventricular septum; PS = pulmonary stenosis.

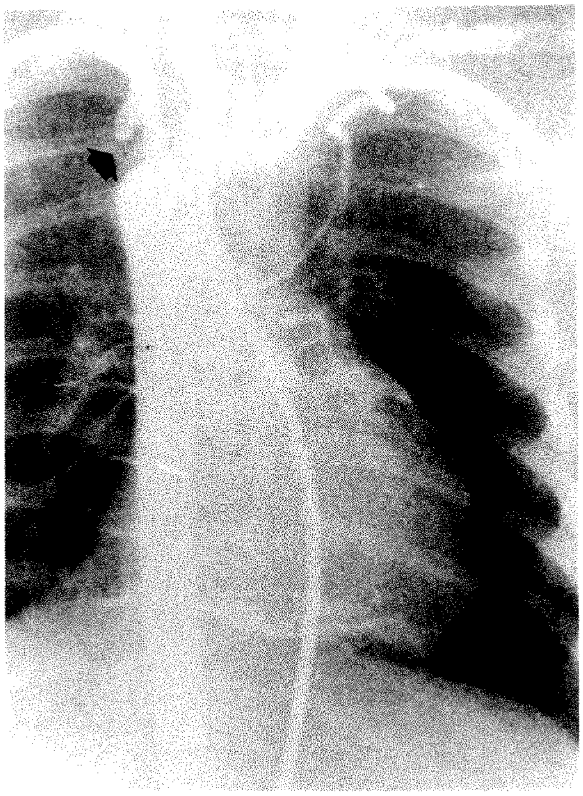

Fig 1. Aortogram showing the right conduit occluded by a thrombus (arrow)*, which at postmortem examination was found to have originated at the level of the incision made in the conduit at reoperation.*

Table 2. Diagnoses of Patients Having Elective Postoperative Angiograms following Modified Blalock-Taussig Shunts (Gore-Tex)

Diagnosis	No. of Patients
Tricuspid atresia + PS	4
Concordant transposition	3
Pulmonary atresia + VSD	8
Tetralogy of Fallot	6
Pulmonary atresia + IVS	2
Univentricular heart + PS	3
Miscellaneous	3
Total	29

Abbreviations same as for Table 1.

Table 3. Angiographic Findings 5 to 29 Months (Mean, 15.6) Postoperatively in 29 Patients with Modified Blalock-Taussig Shunts (Gore-Tex)

Conduit Size (mm)	No. Patent	No. Occluded	No. Irregular	No. of Stenosed Subclavian Anastomoses
4	8	1	3	3
5	2	0	0	0
6	18	0	1	0
Total	28 (97%)	1 (3%)	4 (14%)	3 (10%)

exercise tolerance and exhibited good shunt murmurs on physical examination. No clear correlation emerged between the degree of cyanosis or exercise tolerance and shunt function. A moderate degree of congestive heart failure necessitated treatment with digoxin and diuretics in 6 patients (20.7%). In addition to the modified shunt, 2 of these patients had patent Waterston shunts and 2 had multiple aortopulmonary collateral vessels. During the initial outpatient follow-up period, the shunt murmur diminished in 1 patient and disappeared in another. The former had had a severely stenosed shunt at cardiac catheterization, and in the latter the shunt was occluded.

Angiocardiographic findings are summarized in Table 3. The Gore-Tex prosthesis was said to be irregular if a filling defect was seen in two dimensions or if more than one such defect was present (Fig 2); this change occurred most frequently in 4 mm shunts. A similar appearance resulted from kinking of an

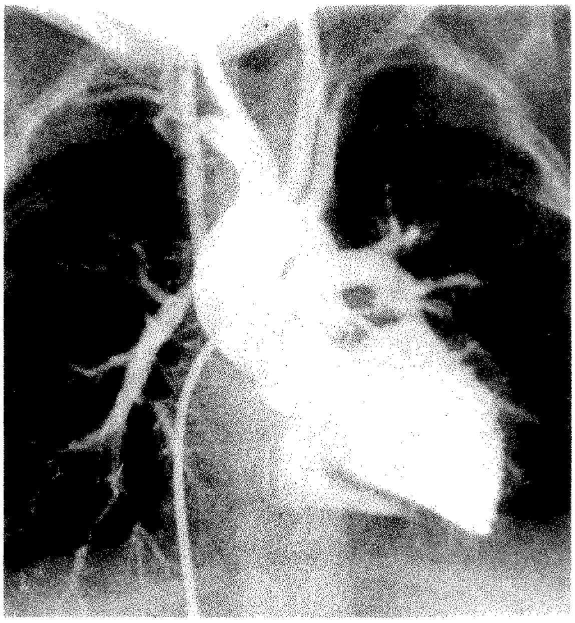

Fig 2. Irregular contour (arrow) *of a 4 mm Gore-Tex conduit.*

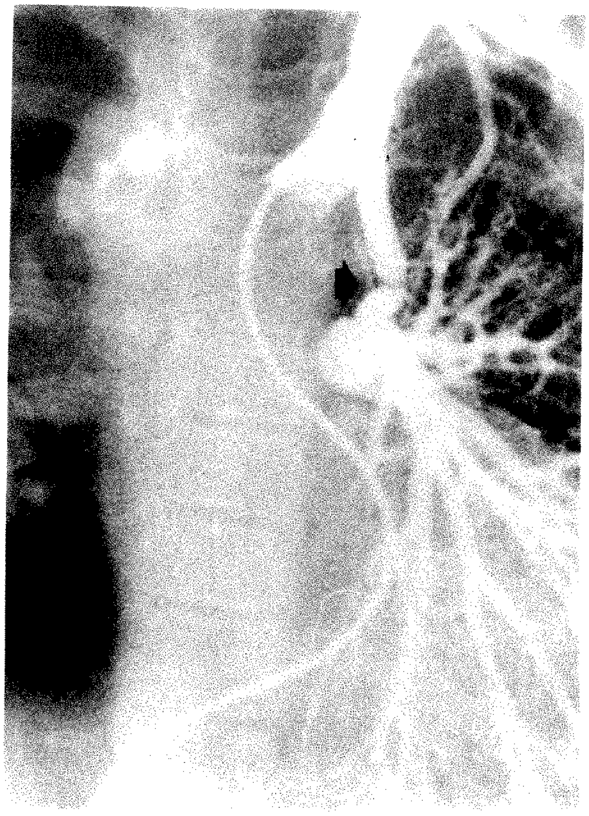

Fig 3. Kinking (arrow) *of an elongated 6 mm Gore-Tex shunt where a stay suture had been placed to anchor the shunt on the anterior pericardium. This was done to improve access during subsequent complete repair from a midline sternotomy.*

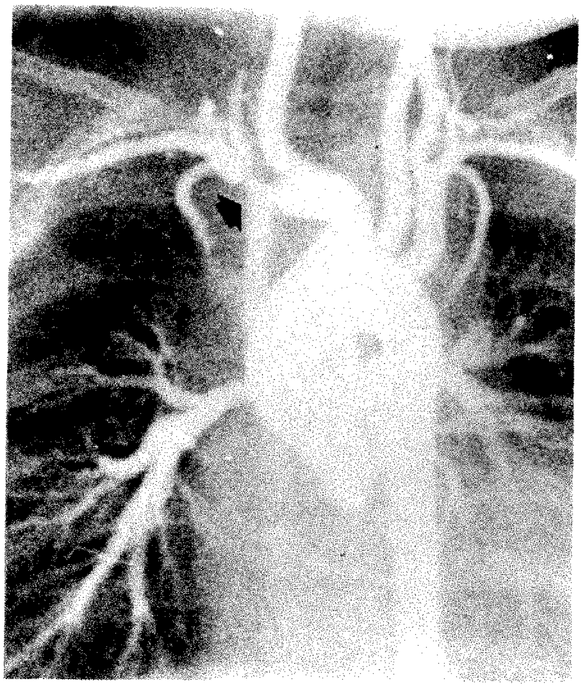

Fig 4. Stenosis (arrow) *of the subclavian anastomosis of a modified 4 mm Blalock-Taussig anastomosis performed during the first week of life of the patient.*

elongated shunt in which a stay suture had been placed to anchor the shunt in the anterior mediastinum so as to improve access during subsequent repair through a midline sternotomy (Fig 3). Stenosis of the subclavian anastomosis (Fig 4) was seen in 3 conduits, all 4 mm, performed in the first week of life. The shunt was occluded in an infant with pulmonary atresia, ventricular septal defect, and hypoplastic confluent pulmonary arteries who was perfused through large collateral arteries. This patient underwent a right modified Blalock-Taussig anastomosis at the age of 5 months. When restudied 18 months later, the shunt was seen to be occluded. The patient then received a central shunt, which also failed to improve her status.

Growth of the pulmonary arteries relative to that of the descending thoracic aorta is summarized in Table 4. The mean increase in this ratio was 0.19 ± 0.308 on the right side and 0.19 ± 0.292 on the left (p = 0.10 and 0.09, respectively). Considering just the 6 patients shunted as neonates, the mean increase was 0.28 ± 0.287 on the right (p = 0.007) and 0.32 ± 0.173 on the left (p = 0.006). However, in an 8-month-old boy with tetralogy of Fallot whose arteries failed to grow, there was stenosis of the shunt and narrowing of a previously patent ductus arteriosus at the time of reinvestigation. Despite irregularities in the 4 mm shunts, the majority of patients in whom this size prosthesis was used showed a marked increase in diameter of the pulmonary arteries.

Among the 28 patients with patent shunts, 1 with a stenosed subclavian anastomosis had increasing cyanosis and was not considered suitable for repair at the time of reevaluation; a second modified shunt procedure was done successfully. Four patients have undergone successful palliation for lesions that are not correctable. Another 4 have undergone repair of the defect, and 17 are presently awaiting repair with adequate palliation. (No difficulty has been encountered in ligating the shunt at the time of repair.) Two 6 mm shunts were recovered 15 and 28 months after implantation,

Table 4. Changes in the Right and Left Pulmonary Arteries Relative to the Aorta Following Modified Blalock-Taussig Shunt

Diagnosis	Age	Shunt Size (mm)	Diameter Changes in RPA/DAo	Diameter Changes in LPA/DAo
Tetralogy of Fallot	3 d	4	+0.57	+0.20
Tetralogy of Fallot	12 d	4	+0.52	+0.10
Tricuspid atresia	2 d	4	−0.02	+0.45
Pulmonary atresia + VSD	4 d	4	+0.36	+0.27
Pulmonary atresia + IVS	2 d	4	−0.14	+0.31
Pulmonary atresia + IVS	4 d	4	+0.29	+0.58
Tetralogy of Fallot	8 mo	4	−0.33	−0.38
DORV + banded pulmonary artery	2 yr	5	+0.38	+0.30
Univentricular heart + PS	10 yr	6	+0.10	−0.12
Mean change in diameters of pulmonary arteries/DAo = +0.19 ± 0.302[a]				

[a] $p = 0.10$.

RPA = right pulmonary artery; DAo = descending thoracic aorta at level of diaphragm; LPA = left pulmonary artery; DORV = double-outlet right ventricle; other abbreviations same as for Table 1.

respectively, following death at corrective operation. Both shunts had smooth neointima covering the suture lines and the Gore-Tex conduit.

Comment

Because of a high patency rate, improvement in systemic oxygenation, low incidence of pulmonary overperfusion, and satisfactory management at the time of repair, the Blalock-Taussig shunt remains the procedure of choice for most systemic-pulmonary anastomoses. In neonates and infants, however, a small degree of tension caused by a short subclavian artery can easily kink and occlude the pulmonary anastomosis; this applies as well to patients with hypoplastic pulmonary arteries. Also, results of Blalock-Taussig anastomosis are less satisfactory when the anastomosis is performed on the side of the aortic arch. Early results with the modified Blalock-Taussig anastomosis in these situations have been encouraging.

Angiography in this study confirmed the clinical impression of a high patency rate in Gore-Tex shunts between the subclavian and pulmonary arteries between one and three years postoperatively (97% patency rate among patients restudied electively). Clinical observation was a good guide to pulmonary perfusion. In those patients in whom cyanosis increased, exercise tolerance decreased, or shunt murmurs disappeared, stenosed or occluded shunts were encountered. Reinvestigation is indicated for such patients, particularly in the early postoperative period, because occlusion at the subclavian anastomosis can be successfully managed by reoperation. Of particular importance was the rapid occlusion of 1 shunt following exploration. Suture in PTFE tubing has caused thrombosis of a 5 mm central shunt [13], and thrombosis has been initiated experimentally by needle puncture of a graft [21]; it would appear that any damage to the prosthesis predisposes to occlusion. Persistent cyanosis postoperatively can be related to pulmonary venous obstruction, however, and surgical exploration of the shunt should not be undertaken without angiographic evidence of shunt failure.

In spite of the 97% patency rate found on elective angiography, the high incidence of irregular or stenosed shunts—particularly among neonates with 4 mm conduits—is cause for concern. Theoretical predictions of a high patency rate for small-caliber PTFE conduits were based on its nonwettable electronegative surface [8, 22] and a porosity that allows limited endothelialization by a viable neointima [26, 57]. These predictions have been substantiated in experimental work of limited duration [4, 10, 14, 21] and in clinical use for hemodialysis [21], reconstructive peripheral vascular surgery [3, 6, 24, 25], and replacement of the portal vein [18] as well as in small numbers of cerebral [23, 25] and myocardial [15, 16, 20, 27] revascularizations. However, follow-up beyond two years has been reported only with 6 mm grafts, for which life-table analysis showed a cumulative patency of 76% at 28 months in lower limb revascularization. Our experience with late failures in patients with a modified Blalock-Taussig anastomosis to date is insufficient for determining if they result from a technical error that predisposes to intimal thickening, from the characteristics of the graft itself, or from their use in neonates. The failures do serve to emphasize the need for careful patient follow-up, however, with awareness that clinical deterioration has been accompanied by neointimal changes and narrowed anastomoses after 12 to 18 months.

We now believe that the success rate of the modified Blalock-Taussig shunt would be increased by using conduits of at least 5 mm in diameter even in neonates. If the shunt can be performed on either side, our preference in neonates is for the side of the aortic arch, where there is less risk of damaging the recurrent laryngeal nerve and where the length of the subclavian artery before its branching tends to be greater. In addition, given the possible need for a second shunt procedure before repair is carried out, it would seem advisable to use the side of the arch for the modified shunt in neonates, thus preserving the other subclavian artery for a classic Blalock-Taussig shunt when the child has grown.

Judging from the angiocardiographic findings in patients in whom 4 mm grafts were used, it is clear that by the age of 1 year the diameter of the subclavian artery is similar to or even greater than that of the conduit. Therefore, our expectation that flow would increase as the patient grew is not applicable for more than a few months when a 4 mm graft is utilized. This is another reason for using conduits of at least 5 mm, even in neonates, when the palliative operation is expected to last for several years.

The importance of the pulmonary arteries in achieving successful repair of congenital heart defects is generally recognized [1], and palliative operations in both tetralogy of Fallot [2, 7, 11] and pulmonary atresia with ventricular septal defect have been found to increase the size of these vessels. While previous shunts and discontinuous pulmonary arteries precluded measurements in most patients reinvestigated in this series, the small number of patients in whom this estimation was possible showed an increase similar to that observed after Blalock-Taussig shunting in tetralogy of Fallot [7]. Among neonates this increase in size of the pulmonary arteries was comparable to that achieved with the Waterston anastomosis [2]. Equally important was the preservation of the pulmonary arteries after a modified Blalock-Taussig anastomosis and the fact that in no case has kinking or distortion of the vessel occurred.

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Discussion

DR. HENRY T. BAHNSON (Pittsburgh, PA): I am grateful to Dr. McKay for presenting this work to us and for the opportunity to read the manuscript. In the third of a century since I helped Dr. Blalock and then was helped by him to do Blalock operations, there have been many alternatives to his original procedure. I think this is one of the most promising.

One of the early harbingers occurred when Denton Cooley, then in Houston, reported to his chief that he had been successful in doing a Blalock anastomosis in a 6-day-old child. Operations at that age now are commonplace, often with the help of magnification and other techniques that have been honed by experience with coronary artery bypass. At present, one of the major targets of the Blalock, or systemic pulmonary, shunt is the newborn.

Our experience at the University of Pittsburgh, like that of others, has invariably shown that when comparison is made, the Blalock shunt comes out best in terms of patency, freedom from congestive failure, relief of cyanosis, and freedom from the need of an additional procedure. In 1979, we used the Blalock shunt exclusively, and a third of them were in patients in the first day of life.

I really have nothing but compliments for Dr. McKay's presentation. I think particularly intriguing is the postulate—for which I believe she is now beginning to get evidence—that a larger than ideal conduit in the newborn may not grow but that the subclavian artery may grow to it, and that the subclavian will continue to govern the size of the shunt. I think this is one of the major reasons why a subclavian shunt does not lead to congestive failure.

The number of operations that this group has reported, nearly half of them since Mr. Stark mentioned this in discussion at this meeting last year, suggests that perhaps they have widened the indications for this type of procedure. It also suggests perhaps that there are some operations in which Gore-Tex is used where previously a direct anastomosis would have been done. This is the basis of my only question. Have you broadened your indications enough to use Gore-Tex in virtually all patients so that you now can study the direct shunt and that done with Gore-Tex in comparable patients? When I use prostheses or vein grafts, it is always in the more difficult patients. Therefore, it has been impossible to compare the direct shunt with one using a prosthesis.

I hesitate to make a technical comment about results that are so good, but it was pointed out some time ago, I think by Dr. Blalock that, at least in his hands, a longitudinal incision in the pulmonary artery seems to lead a little less frequently to narrowing of this artery. It is one of the complications that may arise from any type of systemic-pulmonary anastomosis.

DR. ANTHONY R. MOULTON (Baltimore, MD): Miss McKay is to be commended for a fine presentation of an impressive series. Having spent a year at Great Ormond Street and having had the opportunity to perform some of the procedures described today, I can attest that the use of these prosthetic tubes is quick, easy, and reproducible. Miss McKay has just demonstrated that long-term patency rates are also high.

But Mr. de Leval and Mr. Stark also taught me that a primary Blalock-Taussig anastomosis can be safely and reproducibly created, even in tiny neonates. I would like to underline Miss McKay's statement that the Blalock-Taussig anastomosis therefore remains the shunt of first choice in patients with cyanotic congenital heart disease. There were 20 neonates in the series presented this morning, 13 less than 1 week old, and most of the early deaths were in this group.

Among the infants who had a shunt procedure at the University of Maryland Hospital in the past five months were 7 neonates less than 3 days old. A primary Blalock-Taussig anastomosis was created in all of them, with gratifying rises in the partial pressure of oxygen. The only shunt-related death was in a baby weighing 1,900 gm in whom a prosthetic graft was placed after the Blalock shunt had thrombosed ten days postoperatively during a hypotensive episode. Findings at postmortem examination demonstrated a couple of technical problems that can adversely affect the outcome of the use of prosthetic tubes for shunts in tiny neonates.

In patients with tiny pulmonary arteries, the semirigid prosthetic tube often has a much larger diameter than the pulmonary artery. Mobilization and incision of adequate length must be made in the pulmonary artery. Like Dr. Bahnson, I believe that a transverse incision may not provide adequate length. Though the anterior wall of the pulmonary artery will stretch to accommodate the graft, it may result in flattening of the posterior wall with a decrease in the effective cross-sectional area of the pulmonary artery. Furthermore, because of the relative rigidity of the prosthetic tube, the end of the graft must be fashioned in a semicircular shape because simple beveling of the end may produce an angle that could prevent retrograde flow into the pulmonary artery. This would produce distortion and cause subsequent problems.

Miss McKay has presented exciting results with a procedure that should be added to the armamentarium of all surgeons dealing with the critically cyanotic neonate. However, I think final judgment must await more long-term results and experience at subsequent repair before this becomes a procedure of first choice in all or even most patients.

DR. TIMOTHY J. GARDNER (Baltimore, MD): In support of the experience with Gore-Tex shunts in children presented so nicely here, I will review very briefly our experience with Gore-Tex shunts for the treatment of severe cyanosis in infants and mention our current anatomical preference for shunt placement based on this experience.

In the past two and a half years at the Johns Hopkins Hospital, we have placed Gore-Tex shunts in 30 infants, 16 of whom were neonates at the time of operation. The average age at operation was 5 days. Our early use of Gore-Tex involved central shunting from the ascending aorta to the pulmonary artery. More recently, we have used the descending aorta–left pulmonary artery position or alternately the subclavian–pulmonary artery position for shunts in larger infants.

There were 5 hospital deaths, 2 shunt-related. Both of these deaths occurred when we were using the ascending aorta–main pulmonary artery position. One death was related to severe overflow to the lungs and the other, to a shunt occlusion. There have been 2 late deaths, neither related to the shunt. In both instances, the shunts were patent at postmortem examination. There was one late shunt thrombosis in an infant with tetralogy of Fallot who was successfully repaired. We have no problems with significant congestive heart failure after shunt placement in the descending aortic position. Because of this favorable experience, the descending aorta–left pulmonary artery position has become our shunt position of choice.

DR. JURO WADA (Tokyo, Japan): I enjoyed this beautiful presentation from Great Britain and highly appreciated it. Through 1979 at the Tokyo Women's Medical College, Heart Institute of Japan, we had 59 patients who underwent a shunt operation with use of expanded polytetrafluoroethylene (PTFE) tube. Average age of the patients is 4 years 5 months, and average follow-up is 2 years 8 months.

There were 26 right and 20 left modified Blalock anastomoses done. Overall operative mortality was 10.25% and late death was 3.4% (1.5% per 100 patient-years). Early occlusion (less than a month) occurred in 5 patients and late occlusion in 5, an incidence of 2.2% per 100 patient-years. Graft patency four years postoperatively was 76.6%.

It is my impression that the modified Blalock shunt with PTFE showed late occlusion in increased numbers over time compared with the original Blalock procedure. To close the shunt at the following surgical setting, I do recommend use of a Weck clip, which is easy and timesaving.

DR. MC KAY: I thank all the discussants for their comments. In answer to Dr. Bahnson's question about broadening our indications, we actually have limited them in view of the late results with the 4 mm shunts. We strongly believe that whenever a satisfactory, classic Blalock-Taussig anastomosis can be performed, it is the procedure of choice. The large number of modified Blalock-Taussig shunts this past year reflects a high proportion of neonates and patients with previous operations; but, it still represents less than one-third of all systemic-pulmonary anastomoses done at the Hospital for Sick Children during this period.

I thank Drs. Moulton, Gardner, and Wada for reviewing results from their respective institutions. We agree with Dr. Moulton that technical details assume increasing importance with hypoplastic pulmonary arteries. However, we have not had problems with the transverse pulmonary arteriotomy and can say only that, in our experience, it has given satisfactory results. This includes a number of patients whose pulmonary artery measured 1.5 to 2.0 mm in diameter at the time of operation.

As regards management of the modified Blalock-Taussig shunt at the time of complete repair, we have had experience with 5 patients. On the side opposite to the aortic arch, the shunt was approached as a classic Blalock shunt without difficulty. On the side of the arch, it seemed to lie more anterior than a direct subclavian–pulmonary artery anastomosis, and dissection along the arch did not give good exposure. We identified these shunts from the pulmonary artery. It is also helpful to realize that Gore-Tex feels very firm and may have little pulsation on palpation. In these patients, the shunt was occluded by double ligation with ductus silk. However, we do not know if leaving prosthetic material between the subclavian and pulmonary arteries will result in later distortion of these vessels.

The subclavian artery was selected for the systemic anastomosis for several reasons: (1) its orifice may act as a flow regulator, permitting larger shunts to be used in small infants; (2) the prosthesis lies in a straight line without risk of kinking; (3) the pericardium is not opened; and (4) the shunt is accessible at the time of cardiopulmonary bypass. We would be concerned about the risk of congestive heart failure with a prosthesis from the descending aorta and the chance that these shunts might prove difficult to take down.

Finally, the incidence of 2.2% closure per year reported by Dr. Wada is very much in keeping with our own experience and again emphasizes the need for careful follow-up of these patients.

Systemic-Pulmonary Shunts in Neonates and Infants Using Microporous Expanded Polytetrafluoroethylene: Immediate and Late Results

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Kenneth Zahka, M.D., and B. S. Langford Kidd, M.D.

ABSTRACT **Thirty infants with various types of cyanotic congenital heart disease underwent systemic–pulmonary artery shunts with a microporous polytetrafluoroethylene (PTFE) graft between May, 1976, and July, 1979. Sixteen of them were less than 1 month old, and the average age of the neonates was 5.3 days. There were no operative deaths and 5 hospital deaths, 2 related directly to the shunt. Five patients required early revision of the shunt. Relief from cyanosis was achieved in each patient. Twenty-five patients have been followed up to three and one-half years. There have been 2 late deaths and one late occlusion of the shunt. One patient outgrew the shunt and required secondary shunting procedures. Three of 30 patients have evidenced mild congestive heart failure, which has responded to digitalis. Because of the reliability and excellent late patency of the PTFE prosthesis, we consider it to be superior to a central or Potts shunt for relief from cyanosis in the neonate and infant, and as reliable as a Blalock-Taussig shunt.**

In recent years, there has been a trend to early repair of cyanotic congenital heart disease. However, there still remains a need for improving pulmonary blood flow by systemic–pulmonary artery shunts in neonates and infants with complex congenital heart disease who are not favorable candidates for intracardiac repair. The standard systemic–pulmonary artery shunts, including the Blalock-Taussig, Potts, or Waterston anastomosis, have been used extensively and successfully in many infants with heart defects requiring increased pulmonary blood flow. Each of these shunts, however, has its limitations. The Potts and Waterston shunts have excellent records for reliability and patency. However, there have been reports of left ventricular failure and increased pulmonary vascular disease with their use [4, 8, 9]. Moreover, the Potts and Waterston shunts have proved to be difficult to take down at the time of intracardiac repair [2, 10]. The Blalock-Taussig shunt is the most favored of the systemic–pulmonary artery shunt procedures, and its successful use has been reported in neonates [1, 11]. Occasionally, however, because of technical or anatomical considerations, a Blalock-Taussig shunt cannot be constructed. In such patients a satisfactory substitute has been the use of expanded polytetrafluoroethylene (PTFE) grafts [3, 5, 7]. This report describes our experience in 30 neonates and infants with a systemic–pulmonary artery shunt using a PTFE prosthesis.

Material and Methods

Between May, 1976, and July, 1979, 30 infants less than 2 years old underwent a systemic–pulmonary artery shunt with a PTFE graft. Sixteen patients were less than 30 days old (average age, 5.3 days). All patients had complex cyanotic congenital heart disease and were markedly desaturated at the time of diagnosis. Arterial oxygen saturation averaged 62%. Diagnosis included the following: pulmonary atresia, 6 patients; tricuspid atresia, 8; tetralogy of Fallot, 8; transposition of the great arteries, 5; and pulmonary stenosis, 3 patients. Twenty patients had a descending aorta–pulmonary artery anastomosis; 6 patients had a subclavian or innominate artery–pulmonary artery anastomosis; and 5 patients had an ascending aorta–pulmonary artery anastomosis. Five millimeter shunts were used in 14 patients and 4 mm shunts in 16 patients.

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All neonates with ductus-dependent lesions after cardiac catheterization and diagnosis were started on a regimen of prostaglandin E_1 to assure ductal patency and lung perfusion. After the pH and arterial oxygen saturation stabilized, the patient underwent urgent operative intervention. The chest was opened on the side of the aortic arch. If a large innominate or subclavian artery was encountered, a PTFE shunt was constructed between this vessel and the ipsilateral pulmonary artery. If this vessel was judged to be inadequate in size, a descending aorta–ipsilateral pulmonary artery anastomosis was made. Sutures of 7-0 polypropylene were used for both proximal and distal anastomoses. An alpha-adrenergic stimulator was administered if blood pressure fell below 90 mm Hg, and heparin, 1 mg per kilogram of body weight, was given at the time of shunt construction. No further heparin was administered. In the postoperative period, blood pressure was kept at 90 mm Hg or more and, if necessary, adrenergic stimulators were administered.

Results

There were no intraoperative deaths. Five patients died during hospitalization, and the cause of death is described in the Table. Two of these deaths were attributed directly to the shunt procedure. One patient died of hypoxia resulting from a clotted shunt, and a second patient died of massive congestive heart failure after construction of an ascending aorta–pulmonary artery shunt.

Five patients required early revision of the shunt, and in 3 of them the shunt had been placed in the central position from the aorta to the main pulmonary artery. At the time of shunt revision, a kinked shunt was responsible for these three shunt failures. Each patient surviving hospitalization had an improvement in arterial oxygen saturation. It was measured in each patient immediately after shunt procedures, but could not be compared with preoperative values because 14 of the neonates had been receiving prostaglandin prior to operation. This treatment had improved the arterial oxygen saturation initially.

There is 100% follow-up of the 25 surviving patients from four months to three and one-half years. There have been 2 late deaths. One patient died of heart failure and was found at postmortem examination to have an incompetent atrioventricular valve. The second patient died of unknown causes. At postmortem examination, both patients were found to have patent shunts. One patient required a second shunting procedure fourteen months after the initial shunt because of a rising hematocrit, and 1 patient had a late occlusion of the shunt at six months and underwent intracardiac repair of the defect at that time. The remaining patients have maintained clinical stability.

Hospital Deaths after Creation of a Polytetrafluoroethylene Systemic–Pulmonary Artery Shunt

Patient No.	Age	Diagnosis	Comments
1	8 mo	Tricuspid atresia, hypoplastic right ventricle, pulmonary valve stenosis	PTFE aorta–MPA 4 mm shunt; shunt kinked and clotted and was revised successfully; severe hypoxia with brain death
2	1 d	Hypoplastic right ventricle, tricuspid atresia, pulmonary valve absent	PTFE aorta–LPA 4 mm shunt; died of heart failure; shunt patent
3	1 d	Single ventricle, pulmonary valve stenosis, dextrocardia	PTFE aorta–LPA shunt; died of pneumothorax; shunt patent
4	7 wk	Tricuspid atresia, pulmonary atresia	PTFE aorta–MPA shunt; died of renal failure; shunt patent
5	14 mo	Pulmonary atresia	PTFE aorta–RPA shunt; died of congestive heart failure

PTFE = polytetrafluoroethylene; MPA = main pulmonary artery; LPA = left pulmonary artery; RPA = right pulmonary artery.

In all survivors, physical examination or postoperative catheterization has demonstrated shunt patency. Clinical status, auscultation, and hematocrit have been used to establish shunt patency in the 15 patients who have not undergone recatheterization. In each of these patients, the shunt has been judged to be patent on physical examination. Postoperative cardiac catheterization has been performed on 10 patients. In 9, shunt patency has been demonstrated.

No specific complications have been related to the use of PTFE. There has been no evidence of aneurysm formation or shunt infection. Mild congestive heart failure occurred in 3 patients and was controlled easily with digitalis. In each of these patients there were complex congenital defects, and the congestive failure could not be definitely related to the shunting procedure. The position or size of the shunt in these 3 patients appeared to have no relation to the presence of congestive heart failure. There is no evidence of increased pulmonary vascular resistance in patients undergoing cardiac catheterization nor are there any physical findings of pulmonary hypertension in the patients being followed by clinical means alone.

Comments

In patients requiring systemic–pulmonary artery shunts for palliative relief from cyanotic congenital heart disease, the Blalock-Taussig shunt remains the preferable choice. This shunt has proved to be an effective method of relieving cyanosis with a low complication rate. The Waterston and Potts shunts devised to supplement the surgical armamentarium have proved to be problematical. The Potts shunt has a high incidence of congestive heart failure and pulmonary vascular changes, and the Waterston shunt also has been associated with a high incidence of congestive heart failure. In addition, the Waterston shunt frequently has been demonstrated to cause distortion of the pulmonary artery, which creates problems at the time of intracardiac repair, often requiring reconstruction of the pulmonary artery.

While the Blalock-Taussig shunt is preferable, there are circumstances that occasionally make its use difficult or less than ideal. In small infants, the size of the subclavian artery may be inadequate to provide enough increase in pulmonary blood flow to sustain life. In patients with aberrant subclavian arteries, the shunt is less than adequate. In 1973, Matsumoto and colleagues [6] described the use of PTFE as an arterial substitute in dogs, and in 1976, Gazzaniga and associates [3] reported the use of PTFE for construction of aortopulmonary shunts. PTFE is an ideal vascular substitute for use in small infants and neonates. It is light, requires no preclotting, and has been demonstrated to have a porosity that allows tissue ingrowth and formation of a pseudointima. The material can be penetrated easily with a 7-0 needle, which is satisfactory for construction of arterial anastomoses in small arteries.

Gazzaniga and co-workers [3] initially reported the use of PTFE shunts in a central position, that is, from the ascending aorta to the main pulmonary artery. In 5 of our patients, we used this central approach. It has the advantages of providing blood flow equally into both pulmonary arteries. In our experience, however, it sometimes can be difficult to obtain the proper length of the shunt, and three of the shunts failed because of a kinked graft. Subsequently, in the remaining 26 patients, we used a thoracic approach to construct the systemic–pulmonary artery shunts. In 20 we used the descending aorta–pulmonary artery interposition of the shunt (Fig 1). This is an easy technical procedure. It enables the surgeon to use a straight graft which is shorter than the length of graft used for a central approach because it does not require looping of the graft. This avoids the problem of kinking and also diminishes resistance within the conduit because of a reduced length. In 6 patients, a subclavian or innominate–pulmonary artery anastomosis was used (Fig 2). We believe this may be the procedure of choice if the subclavian or innominate artery is of sufficient size to allow the surgeon to technically perform an interposition PTFE shunt. Theoretically, the surgeon can utilize a 4 or 5 mm shunt with potential for the subclavian artery to increase in size as the child grows and thus to increase the flow through the shunt.

Advantages to the use of PTFE in construct-

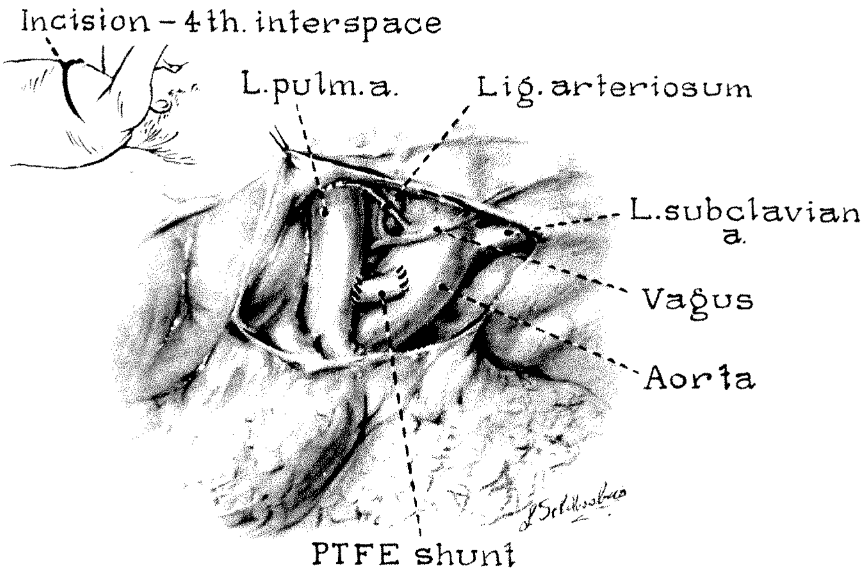

Fig 1. Microporous expanded polytetrafluoroethylene (PTFE) prosthesis interposed between the descending thoracic aorta and the left pulmonary artery. Polypropylene 7-0 sutures are used for the anastomosis.

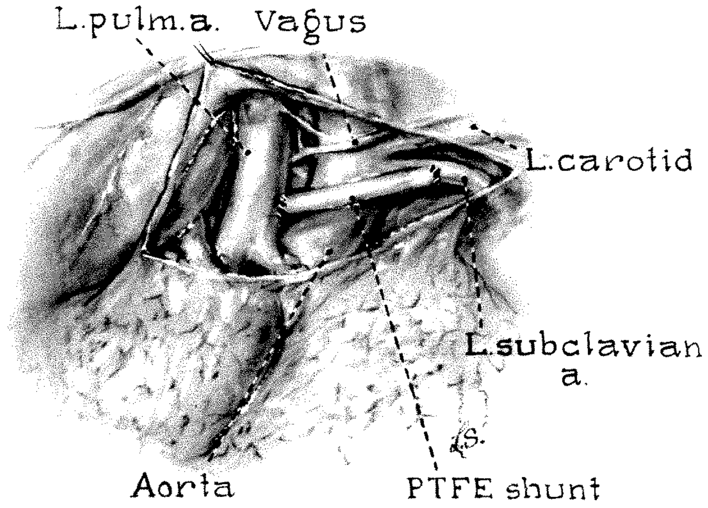

Fig 2. Microporous expanded polytetrafluoroethylene (PTFE) prosthesis interposed between the left subclavian artery and the left pulmonary artery.

ing a systemic–pulmonary artery shunt are several. A shunt with a consistent size can be constructed without regard to other anatomical considerations. We have found the use of 4 and 5 mm shunts to be adequate in infants and neonates. Late patency with this type of shunt procedure has been good, and there is a low incidence of kinking of pulmonary arteries. This should make the PTFE shunt easier to manage at the time of repair than the Waterston or Potts shunt. Placement of the PTFE shunt from the descending aorta or subclavian artery to the pulmonary artery rather than the use of a central type of PTFE shunt has provided good late patency in our patients and has avoided violation of the mediastinum, which may be advantageous when repair is necessary.

The theoretical disadvantages to the use of foreign material have not been a problem in our patients or in other reported series. The ultimate patency of any new type of prosthetic device can be judged only when sufficient time has elapsed. The follow-up on our patients has been relatively short. At the present time, the PTFE shunt should be considered for infants and neonates who require a systemic–pulmonary artery shunt and in whom the Blalock-Taussig shunt is not anatomically feasible or has failed. The reliability, excellent late patency, and relatively low incidence of serious complications make the PTFE systemic–pulmonary artery shunt an attractive substitute.

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Notice from the Southern Thoracic Surgical Association

The Twenty-seventh Annual Meeting of the Southern Thoracic Surgical Association will be held at the Greenbriar, White Sulphur Springs, WV, Nov 13–15, 1980. There will be a $100 registration fee for nonmember physicians except for guest speakers, authors and co-authors on the program, and residents.

Applications for membership should be completed by Sept 1, 1980, and forwarded to E. P. Smith, Jr., M.D., 425 S Bath Club Blvd, N Redington Beach, FL 33708.

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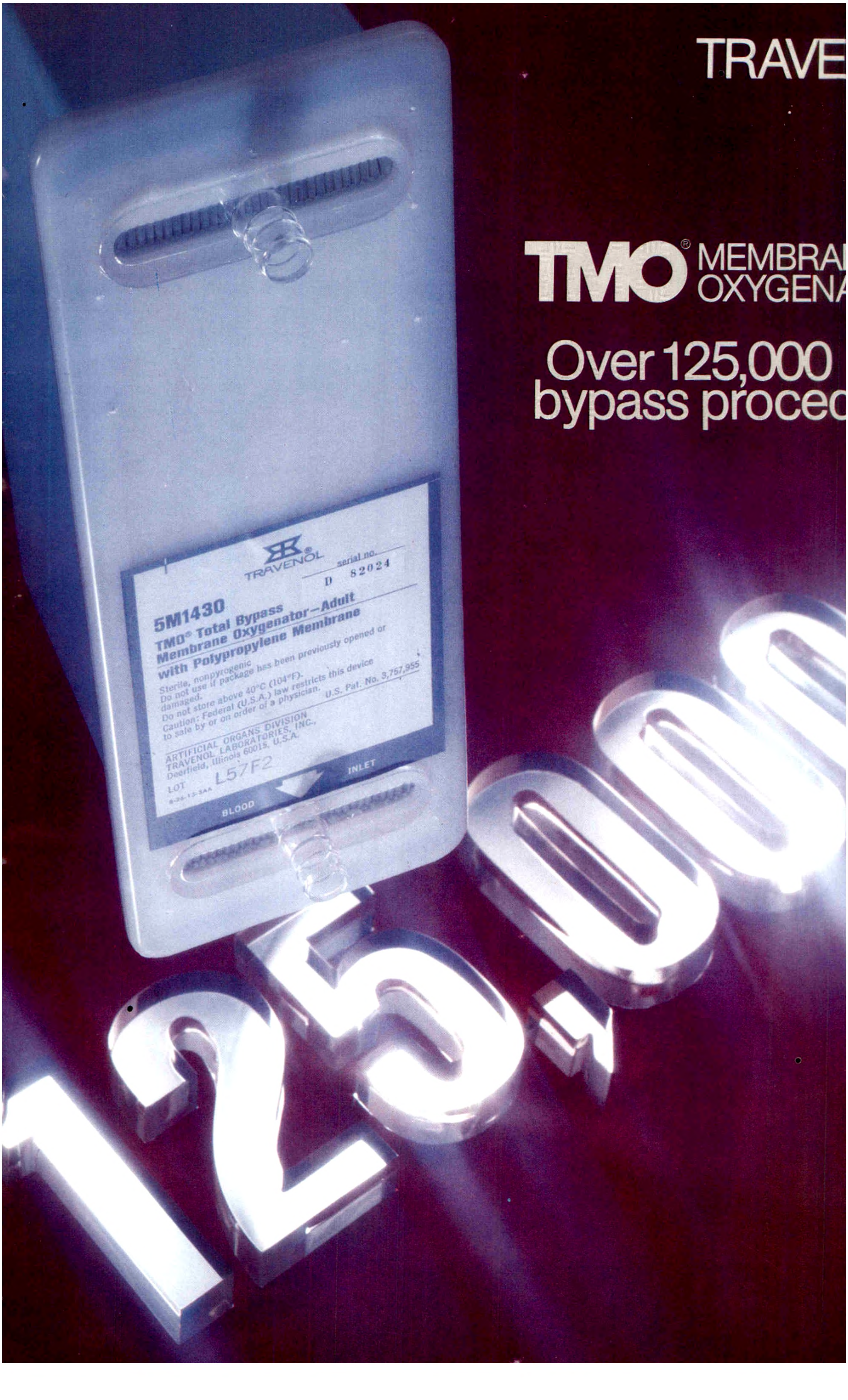
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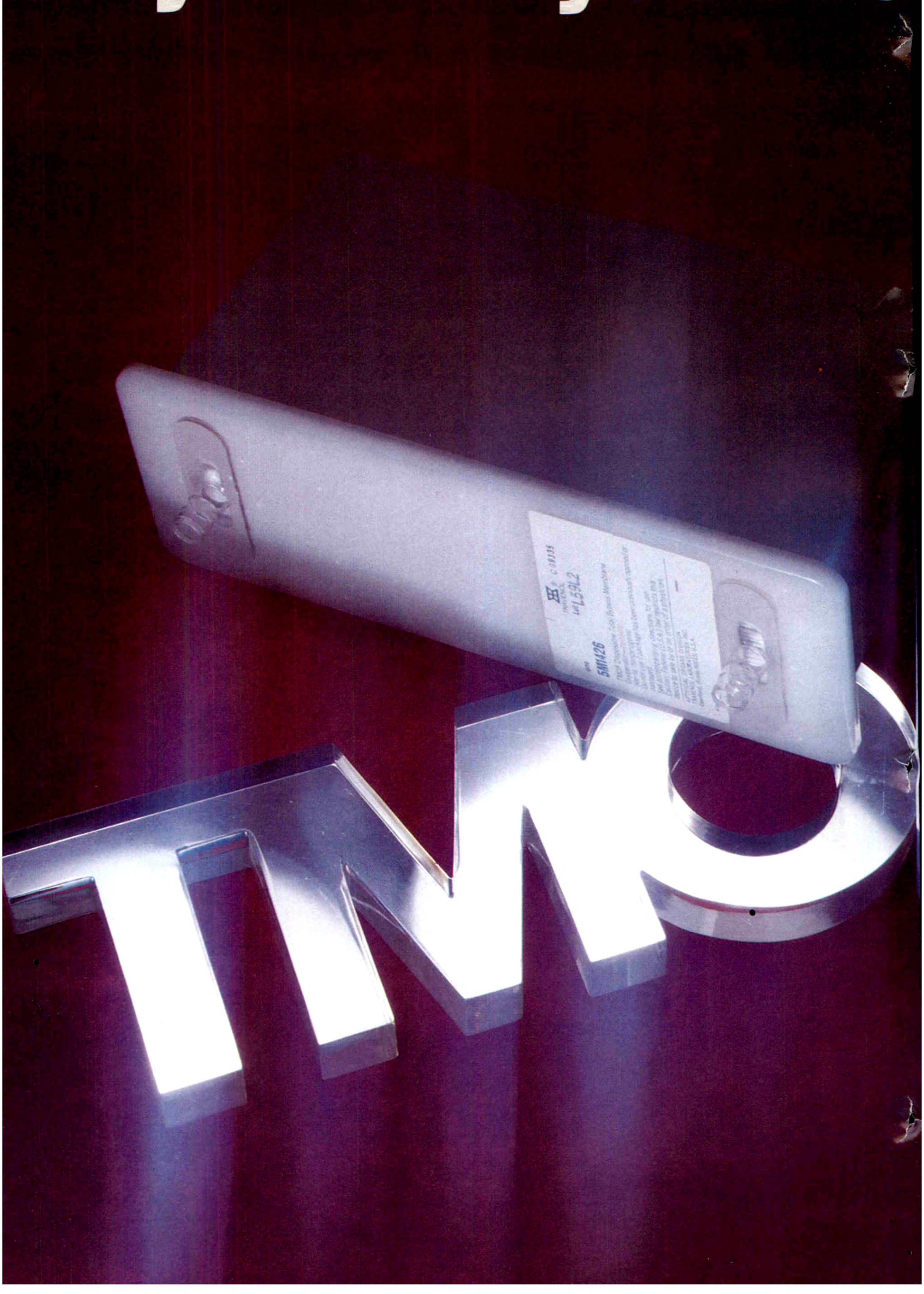

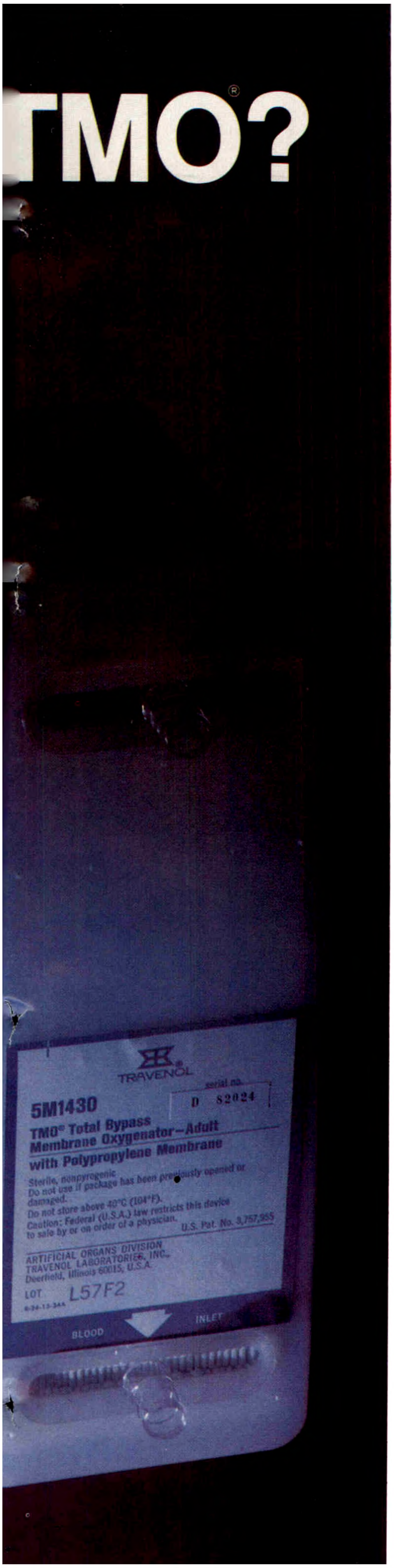
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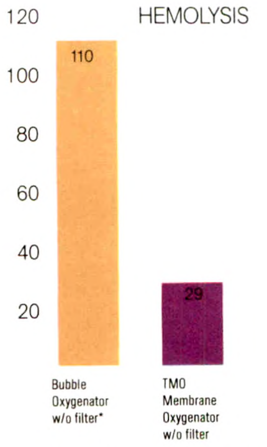

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No. of cases – TMO Oxygenator 65
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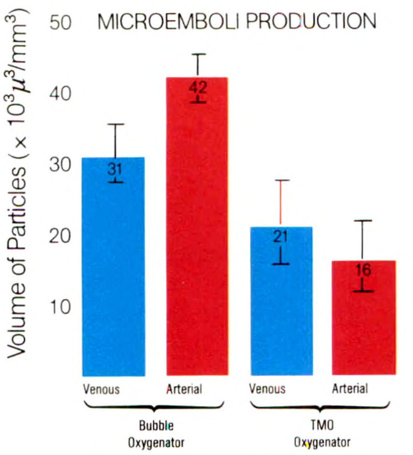

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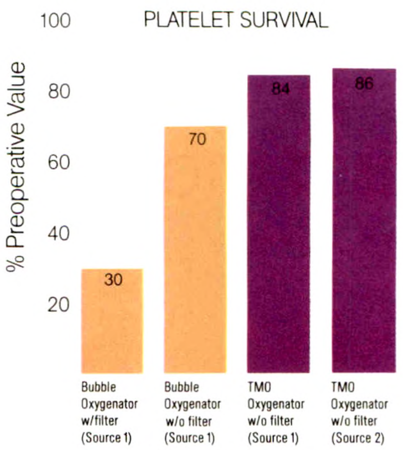

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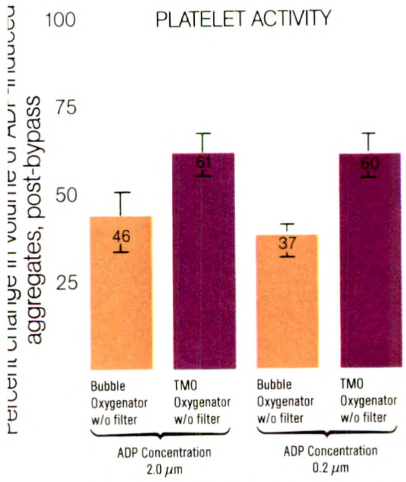

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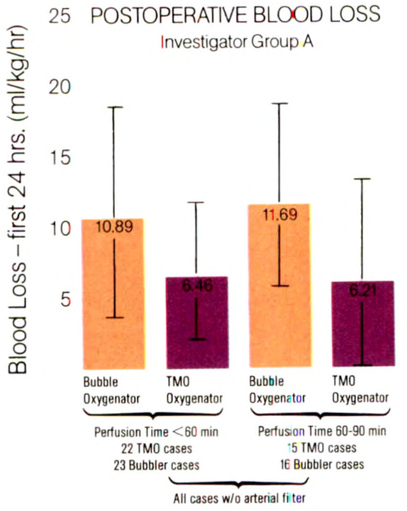

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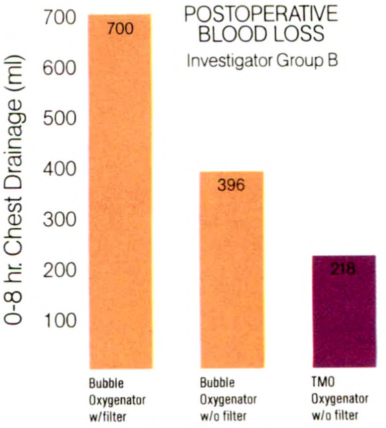

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NDICATIONS

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WARNINGS

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Experience with Repair of Complete Atrioventricular Canal

Frank M. Midgley, M.D., Frank M. Galioto, M.D., Stephen R. Shapiro, M.D.,
Lowell W. Perry, M.D., and Lewis P. Scott, M.D.

ABSTRACT **Twenty-nine patients at our institution have undergone repair of complete atrioventricular canal since 1969. There were 3 operative and 5 late deaths, 4 of which were of infectious etiology. Age at operation ranged from 2 months to 12 years (mean, 50 months). Weight ranged from 3.6 kg to 30 kg (mean, 12 kg). Before repair, catheterization studies revealed pulmonary hypertension in all patients with unobstructed pulmonary arteries. Pulmonary to systemic flow ratio ranged from 1.5 to 10.6 (mean, 3.5). Pulmonary vascular resistance (PVR) ranged from 0.7 to 21.7 (mean, 5.3) Wood units/m^2. At repair, 14 patients had Rastelli type A anatomy, 14 had type C, and 1 patient had a variant with crossing chordae and double-outlet right ventricle (DORV).**

Postoperative catheterization has been done in 16 patients 2 months to 8 years (mean, 30 months) after repair. One patient had residual ventricular shunting and later underwent successful repair. A 2-year-old patient had severe mitral regurgitation and died following mitral valve replacement. One patient required a permanent pacemaker. The 21 surviving patients have been followed from 7 months to 10 years 7 months and have excellent hemodynamic status. Long-term studies are needed to assess the ultimate effect on patients with high PVR.

Complete atrioventricular (AV) canal is a congenital defect for which definitive repair has become increasingly successful [2, 3, 6, 10, 14, 15, 24]. Infants and children with this defect frequently are seriously ill with uncontrollable heart failure and recurrent, progressive pulmonary disease. Additionally, they are subject to the early development of pulmonary vascular obstructive disease. Because of these factors, the trend is toward early primary repair of complete AV canal defects in infancy [1, 11].

The purpose of this paper is to review the surgical experience with repair of complete AV canal at Children's Hospital National Medical Center during the 10 years ending June, 1979, in order to emphasize the clinical features and physiological factors that determine the most favorable time for proceeding with repair.

Material and Methods

Between 1969 and 1979, 29 patients underwent repair of complete AV canal at Children's Hospital National Medical Center, 27 of them since 1974. At the time of operation, the patients ranged from 2 months to 12 years old (mean, 40 months) and weighed from 3.6 kg to 30 kg (mean, 12 kg). There were 12 boys and 17 girls. Twenty patients (69%) had Down's syndrome.

Seven patients were 2 to 12 months old (mean, 5.7 months) with a mean weight of 4.6 kg. Nine patients (31%) had had twelve prior palliative procedures: pulmonary artery banding in 5; ligation of patent ductus arteriosus (PDA) in 4; and Blalock-Taussig shunts in 3. Nine patients underwent elective operation. In the remaining 20 patients, the indications for operation were failure to thrive, refractory congestive heart failure, or progressive pulmonary vascular obstructive disease.

Preoperative Cardiac Catheterization

The diagnosis of complete AV canal was established in all 29 patients by cardiac catheterization and cineangiography. Five patients had previously placed pulmonary artery bands, and 2 had severe infundibular and valvular pulmonary stenosis.

In the 22 patients with unobstructed pulmonary arteries (Group 1), the pulmonary to systemic flow ratio (QP/QS) ranged from 1.5 to 10.6 (mean, 3.5), and all had severe pulmonary

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hypertension with a pulmonary artery to systemic artery systolic pressure ratio (PA/Ao) equal to or greater than 0.6. In the 7 patients with obstructed pulmonary arteries (Group 2), the QP/QS ranged from 0.5 to 2.4 (mean, 1.3), and the PA/Ao was 0.3.

In Group 1, pulmonary vascular resistance (PVR) in room air ranged from 0.7 to 21.7 (mean, 5.3) Wood units/m^2. Eleven or 50% of the patients in Group 1 had PVR in excess of 4 Wood units/min/m^2 in room air. Following administration of oxygen and Priscoline (tolazoline), 5 (45%) of the 11 persisted with PVR in excess of 4 Wood units, though marked lability of pulmonary vasculature was demonstrated. PVR was elevated in only 1 patient in Group 2 and returned to normal following the administration of oxygen and Priscoline.

Atrioventricular valve insufficiency was mild in 17 patients, moderate in 4, and severe in 2. It could not be assessed by angiography in 6 patients.

Associated lesions included PDA in 5 patients, secundum atrial septal defect (ASD) in 7, left superior vena cava to the coronary sinus in 3, left superior vena cava to the left atrium in 1, and double-outlet right ventricle (DORV) in 1. Two patients had coronary artery anomalies consisting of single origin in 1 and a high origin of the right coronary artery from the left side of the ascending aorta in the other.

Surgical Techniques

Twenty-eight procedures were performed through a midsternotomy incision with conventional cardiopulmonary bypass and moderate (27°C) hypothermia. Intermittent aortic cross-clamping with maximum continuous clamp time of 18 minutes was used in 22 patients, while hypothermic cardioplegia was used in the last 6 patients. The duration of cardiopulmonary bypass ranged from 65 to 165 minutes (mean, 102 minutes), with total aortic cross-clamp time of 19 to 74 minutes (mean, 42 minutes) in the intermittent cross-clamp group and 55 to 82 minutes (mean, 67 minutes) in the cardioplegic group. One patient had repair under profound hypothermia and circulatory arrest, the arrest period being 46 minutes. Left ventricular (LV) vents were placed through the LV apex. Five PDAs and three Blalock-Taussig shunts were ligated prior to institution of cardiopulmonary bypass.

Surgical anatomy was of Rastelli type A in 14 patients, type C in 14 patients, and variant type with DORV in 1 patient [18]. Repair in the patients with types A and C were based on the methods described by Rastelli and colleagues [19] with modifications. When present (7 patients), the secundum ASD was joined to the primum ASD by excision of intervening tissues. When necessary, the common mitral–tricuspid valve leaflets were incised to the junction of the AV valve annulus and the crest of the ventricular septal defect (VSD). The mitral cleft was repaired with 4-0 figure-of-8 Polydek sutures. The edges of the AV valves were everted when possible as the sutures were placed. Pledgets and horizontal mattress sutures of 3-0 Polydek were then placed along the right side of the crest of the VSD and passed through the lower edge of an appropriately tailored, stretch Dacron patch. This single patch was utilized to close both the VSD and ASD elements of the defect. The reconstructed mitral valve was attached with horizontal mattress sutures across the midportion of the Dacron patch at an appropriate level to conform with the AV valve plane. Tricuspid elements, when available, were included in the sutures.

Before the repair was completed by closing the ASD, saline solution was instilled through the LV vent to evaluate the adequacy of repair of the mitral valve cleft and the suspension and reconstruction of that part of the mitral annulus as represented by the patch. If necessary, additional sutures were placed in the cleft to minimize the degree of mitral regurgitation. In 1 patient, a standard annuloplasty suture was utilized to obliterate significant mitral regurgitation detected at the posterior medial commissure. The adequacy of repair being assured, the ASD was closed, utilizing the upper portion of the patch and continuous suture technique.

One 7-month-old, 5.2-kg patient with DORV had chordae tendineae extending from the major mitral and tricuspid portion of the anterior common leaflet to a papillary muscle in the left ventricle. Valve leaflet division was planned so as to include all the chordal apparatus with the newly constructed anterior leaflet of the mitral valve. Modification of the VSD portion of the patch facilitated tunneling of the LV outflow to the dextroposed aorta. Two patients required extensive reconstruction of the right ventricular outflow tract (RVOT), 1 by an outflow patch from the right ventricle to the left pulmonary artery and the other with a porcine-valved conduit. Five patients had debanding of the pulmonary artery with pulmonary arterioplasty utilizing a composite Dacron pericardial patch. Pressures measured immediately after repair documented the adequacy of reconstruction in all instances.

All patients received respiratory support for at least three days postoperatively. Cardiotonic support was required for 2 to 36 hours in 22 (76%) of the patients. Nitroprusside was used in the early postoperative period for prophylactic afterload reduction in the last 6 patients.

Results

Operative Mortality

Three (10%) of the 29 patients died within thirty days of operation (Table 1). All 3 patients had Down's syndrome. One was a 7-month-old infant with a preoperative history of recurrent pneumonia, congestive heart failure, and failure to thrive. He died of low cardiac output 36 hours postoperatively. The second patient, 2 years 9 months old, died of uncontrollable tachyarrhythmia 10 hours postoperatively. She had undergone extensive RVOT reconstruction for congenital infundibular and valvular pulmonary stenosis. The third patient, 3 years old, died 48 hours postoperatively of progressive right heart failure. At postmortem examination, all had intact repairs and pulmonary vascular obstructive disease of grades II to V [8].

Considering the relationship of age to operative mortality (Table 2) in the 7 infants less than 12 months old, there was only 1 death (14%).

Table 1. Operative Mortality[a]

					PVR (Wood units/m²)		
Age	Weight (kg)	Type[b]	CPB (min)	Cross-Clamp Time (min)	Room Air	O_2/Priscoline	Other
7 mo	4.9	C	112	41	6	1.9	Gr III
2 yr 9 mo	14.5	C	165	74	2.7	. . .	PS, LSVC to LA, GR II
3 yr	10.0	C	80	25	4.3	1.2	GR V

[a]Operative mortality was 3 out of 29 patients or 10%.
[b]Rastelli classification of anterior common leaflet.

CPB = cardiopulmonary bypass; PVR = pulmonary vascular resistance; GR = grade of pulmonary vascular obstructive disease [8]; PS = pulmonary stenosis; LSVC = left superior vena cava; LA = left atrium.

Table 2. Age at Operation and Outcome

		Operative Mortality		Late Mortality	
Age	No. of Patients	Number	Percent	Number	Percent
3 mo	1	0	0	0	0
3 < 6 mo	2	0	0	2	100
6 < 12 mo	4	1	25	0	0
12 < 24 mo	2	0	0	1	50
2 < 5 yr	14	2	14	2	14
> 5 yr	6	0	0	0	0
Total	29	3	10	5	17

Considering all 9 patients less than 2 years old, there was only 1 operative death (11%). The 5 patients with slight preoperative elevation in PVR following the administration of oxygen and Priscoline all survived operation.

Late Mortality

There have been 5 late deaths on follow-up of 7 months to 10 years 7 months following repair of complete AV canal. Four deaths were due to inflammatory processes in patients with Down's syndrome. One of these patients had a *Hemophilus influenzae* septicemia. The other death occurred in a 2-year-old patient at the time of mitral valve replacement, 3 months following repair of complete AV canal. Postmortem examination was performed in 3 patients and showed an intact repair in each. In the patient with mitral valve replacement, possible obstruction to the LV outflow by a strut of the prosthetic valve was noted.

Postoperative Complications

Important disturbances of cardiac rhythm occurred postoperatively in 2 patients. One patient with tachyarrhythmia and low cardiac output died. Complete heart block occurred in 1 patient and required an epicardial pacemaker.

Four patients needed prolonged respiratory support. Two of them required temporary tracheostomy. Three patients had important postoperative intravascular hemolysis. It contributed to renal failure in 2, both of whom recovered fully. The disappearance of hemolysis occurred 1 to 3 weeks following repair and coincided with pseudoendothelialization of the patch (see Comment). No patient required reoperation for bleeding postoperatively.

Follow-up

The 21 survivors have been followed from 7 months to 10 years 7 months (mean, 3 years 7 months). All are doing well with increased exercise tolerance, lower rate of pulmonary infection, and improved growth.

Postoperative cardiac catheterizations have been performed in 16 patients, 2 months to 8 years following repair. One patient had a QP/QS of 1.1, which increased to 1.7 following administration of oxygen and Priscoline. Since PVR was elevated at 6.9 Wood units in room air but fell to 2.4 Wood units after administration of oxygen and Priscoline and since angiography indicated a periprosthetic VSD, closure of the defect was recommended and was accomplished successfully. The patient was doing well 3 months postoperatively. Another patient had severe mitral regurgitation and subsequently died following mitral valve replacement.

Of the other 14 patients, none had important residual shunting or mitral valve regurgitation (Figs 1, 2). PVR values have remained essentially unchanged from the preoperative levels. In the 11 patients of Group 1, mean PVR was 4.0 Wood units before repair and 4.2 Wood units after repair. PVR values in 5 patients in Group 2 were normal prior to and following operation. Postoperative PA/Ao pressure ratios in both groups ranged from 0.25 to 0.75 (mean, 0.43). At recatheterization, 2 patients had a small, apical diverticulum at the LV vent site.

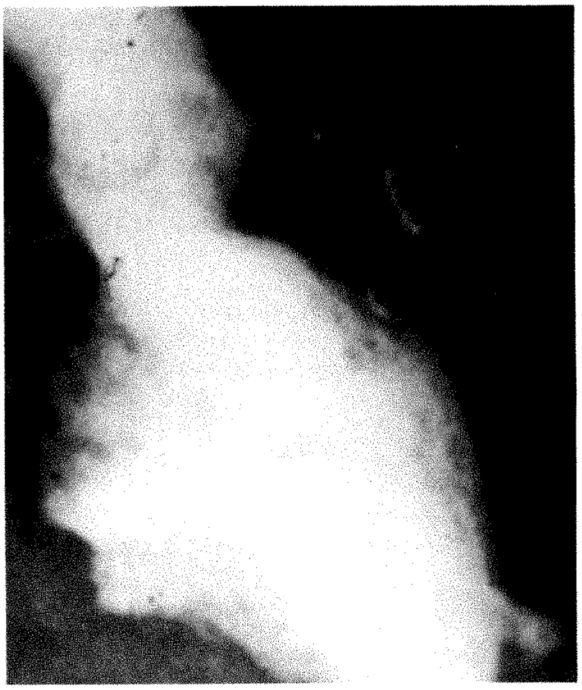

Fig 1. Left ventriculogram from a 19-month-old patient made 13 months following repair of complete atrioventricular canal. Note the intact ventricular septum (lack of right ventricle and pulmonary artery opacification) and absence of mitral regurgitation. Additionally, a small left ventricular apical aneurysm is visible.

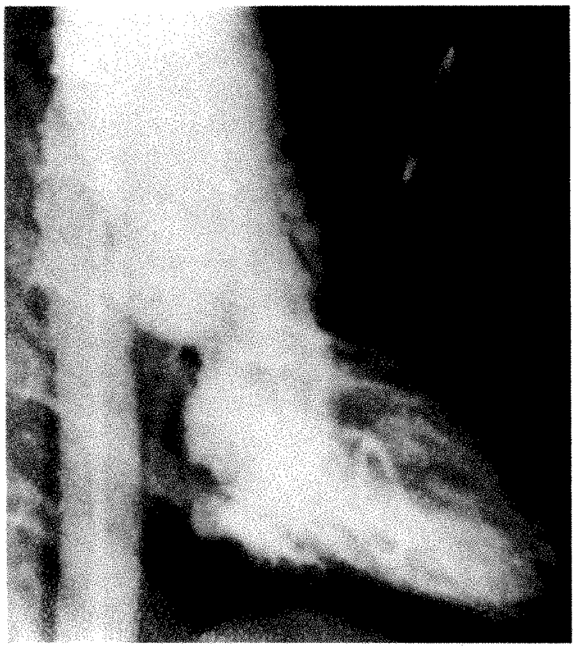

Fig 2. Left ventriculogram from a 6-year-old patient made 2 years following repair of complete atrioventricular canal and severe pulmonary stenosis. The ventricular septum is intact and the mitral valve is competent. Note the support ring of the porcine-valved conduit used for right ventricular outflow reconstruction.

Comment

Of importance in evaluating these results is an appreciation of the natural history of the unoperated form of complete AV canal [2]. Only 54% of patients with untreated complete AV canal survive to 6 months of age and only 35% reach their first birthday. Only 15% live until the age of 2 years and only 4% reach 5 years of age. Mortality is due mainly to severe congestive heart failure and to development of pulmonary vascular obstructive disease. Advanced pulmonary vascular obstructive disease begins to develop during the first year of life [17]. After the child is 2 years of age, advanced pulmonary vascular obstructive disease that fails to improve following repair is encountered commonly.

Knowledge of the anatomical characteristics of complete AV canal is a prerequisite to an accurate and successful repair. Subsequent to the classification of complete AV canal defects on the basis of the common anterior leaflet [18], to the development of surgical techniques for complete intracardiac repair [19], and to improved perioperative care, the initial reports of mortality in excess of 60% [13, 21] were soon supplanted by reports of mortality from 0 to 35% at present (Table 3). Mortality for the

Table 3. Reported Results of Repair of Complete Atrioventricular Canal

		Patients—All Ages			Patients < 1 Year Old			Patients < 2 Years Old		
			Operative Mortality			Operative Mortality			Operative Mortality	
Author	Year	Total Number	Number	Percent	Total Number	Number	Percent	Total Number	Number	Percent
Hardesty et al [7]	1975	17	6	35	...	...	...	...	...	...
Mills et al [15]	1976	8	0	0	0	...	...	1	0	0
McCabe et al [12]	1977	7	2	29	0	...	...	2	0	0
Kahn et al [10]	1977	12	0	0	...	...	...	3	0	0
Mair and McGoon [11]	1977	5	1	20	5	1	20	...	...	...
Berger et al [2]	1978	11[a]	8	73	4	3	75	11	8	73
Culpepper et al [3]	1978	14	3	21	12	3	25	14	3	21
Berger et al [1]	1979	39[b]	8	21	19	6	32	29	6	21
Stewart et al [24]	1979	13	4	31	2[c]	2	100	7	3	43
Total		126	32	25	42	15	36	67	20	30
Midgley et al [this report]	1980	29	3	10	7	1	14	9	1	11

[a] Includes only patients operated on prior to January, 1975.
[b] Includes patients operated on since January, 1975.
[c] Complex lesions.

group of patients less than 2 years old has been noted to range from 0 to 43% with an average of 30%. Mortality for infants less than 1 year old has ranged from 0 to 100% with a mean of 36%. The mortality in our series is compared with that reported by others in Table 3.

Operative mortality does not appear to be related to preoperative levels of PVR providing lability can be demonstrated after the administration of oxygen and Priscoline. However, 2 of the 3 patients who died had advanced pulmonary vascular obstructive disease at postmortem examination despite having labile pulmonary hypertension. Thus, normal PVR levels do not exclude significant pulmonary vascular obstructive disease.

Palliative procedures have been used to ameliorate the physiological effects of complete AV canal [5]. Isolated ductal ligation was used three times in our patients and had no measurable, positive effect on clinical status. Ductal ligation was combined with pulmonary artery banding in 1 patient, and 4 patients underwent pulmonary artery banding alone.

In 3 patients, banding was successful in improving clinical status, protecting the pulmonary vasculature, and delaying the need for definitive repair. Patients were selected for banding on the basis of the degree of AV valve insufficiency, those patients with the least regurgitation being the best candidates. Two other patients, both infants, failed to improve with banding and subsequently underwent successful repair. Overall, operative mortality for patients with complete AV canal who have undergone pulmonary artery banding at our institution since 1965 is 55% (12 of 22) and is similar to that reported by many others [5, 9, 23]. Interestingly, 3 of our 8 survivors of pulmonary artery banding who are presently being followed by us have severe pulmonary vascular obstructive disease despite an adequate pulmonary artery band.

In light of the well-defined natural history of complete AV canal, the knowledge of the poor early and late results of pulmonary artery banding, and the increasingly good results with primary repair, we have adopted a policy of early repair of complete AV canal in infancy. The ease with which the operation is completed in this age group supports this policy. The average age of our last 10 patients was 22 months.

We believe that our patient with DORV and complete AV canal represents the first report of successful repair of this complex lesion in the presence of AV concordance [22]. Successful repair has been reported with AV discordance [4].

We share the opinion that the ultimate success of the operative procedure depends to a great degree on restoring the competency of the mitral valve [2, 19]. To this end, care is taken to assess mitral valve function prior to completion of repair by instilling saline solution into the left ventricle by the LV apical vent. Excellent visualization of the mitral valve is accomplished through the atrial defect. Additionally, the adequacy of the repair of the annulus and the VSD closure can be evaluated. In only 1 patient were we dissatisfied with the availability of tissue for mitral valve reconstruction, and it was this patient who eventually required mitral valve replacement.

Several other details of our operative repair deserve mention. Stretch Dacron is utilized to relieve tension on the suture line in the perioperative period. No pledgets are used either on the mitral cleft or the repair of the annulus, and no dehiscence of the suture lines has been encountered.

The atrial portion of the patch is made as small as possible in order to minimize the hemolysis that may occur due to mitral regurgitation. Nevertheless, 3 of our patients had significant hemolysis and required multiple blood transfusions from 1 to 3 weeks postoperatively until pseudoendothelialization of the patch occurred. This complication has been reported [16, 20], and the cure at some centers has been to line the left atrial side of the patch with pericardium.

No attempts have been made to delineate the conduction pathways. No instances of AV conduction abnormalities have been noted since the third patient of the series.

Postoperatively, we routinely have provided respiratory support and positive airway pressure for 72 hours to allow the pulmonary venous circulation and left atrium to adjust to their new physiological status. Recently, nitroprusside has been used electively for afterload reduction.

Four of our patients died late of infectious disease. All 4 had Down's syndrome, which is known to be associated with an altered immune response.

Follow-up catheterization studies have demonstrated PVR values to be essentially unchanged from preoperative levels. The mean age of these patients at repair, however, was 3 years, which corroborates previous reports demonstrating irreversible pulmonary vascular obstructive disease occurring prior to the age of 2 years [17]. We await the results of recatheterization studies on patients less than 2 years old who are undergoing repair, to determine if early repair will affect the development of pulmonary vascular obstructive disease.

Our experience confirms that restitution of nearly normal hemodynamics can be achieved successfully in the majority of patients with complete AV canal by early repair [2, 3]. The experience from several centers suggests that all patients with pulmonary hypertension, even those who are asymptomatic, should have definitive repair before they are 2 years old and preferably when they are 1 year old.

In summary, our experience supports the contention that repair of complete AV canal is safe and feasible with few residua and that palliation is not indicated in the majority of instances. PVR changes little in the follow-up period if repair is not done before the patient is 2 years old. Normal PVR does not rule out pulmonary vascular obstructive disease. Elevation of PVR in room air is not a contraindication for operation as long as lability is demonstrated. Neither concurrent lesions nor prior palliation present major obstacles to successful repair.

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Discussion

DR. DONALD B. DOTY (Iowa City, IA): Dr. Midgley and associates have presented a very nice series of patients who underwent repair of complete atrioventricular (AV) canal defect. I had the privilege of reviewing the manuscript well in advance. Early and late mortality rates have been very good, and the method of repair has been successful in preventing significant mitral valve incompetence.

Our series from the University of Iowa has produced results in repair of complete AV canal that are similar to those reported by Dr. Midgley. One early death, for an 8% mortality, was due to an error in airway management on the seventh postoperative day. One late death (the first patient in the series) occurred at four months due to mitral valve incompetence and hemolysis. Since that time we have followed the recommendations of Mills and Ochsner pertaining to reenforcement of the septal attachment of AV valves.

Mills and Ochsner use small Teflon felt pledgets to attach the septal portion of the mitral and tricuspid valves to the neoseptum. I believe this is an important technical adjunct and a key to the prevention of dehiscence of the septal leaflet of the AV valve. Perhaps the same reenforcement could be achieved with large-diameter horizontal mattress sutures, but in very young patients the AV valve leaflet tissue is so thin that perforation with small-diameter monofilament suture reenforced with pledgets seems best to me. Would Dr. Midgley please elaborate his thoughts on this technical point.

Dr. Midgley mentioned that the rolled edges of the mitral cleft were everted. I would take exception to this technique if the common AV valve is reasonably competent before operation. I prefer to close the edges of the cleft as they naturally oppose.

Finally, competence of the repaired mitral valve can be tested quite adequately by instilling saline solution through the valve, thereby making left ventricular vent catheters unnecessary. Would Dr. Midgley qualify his opinion with regard to left ventricular venting.

My colleagues and I have been strongly influenced by data from Newfeld and associates, which show that anatomical changes of obstructive pulmonary vascular disease occur early in the natural history of complete AV canal. Here the risk of pulmonary vascular disease increases after the first year of life. I agree with Dr. Midgley that operation should be performed before 2 years of age and preferably at 1 year.

This is reflected in the younger mean age of 18 months in our series compared with 40 months in Dr. Midgley's series. Eleven of the 13 patients in our series were less than 2 years old and none were more than 3 years old. Elevated pulmonary vascular resistance was present in two-thirds of the patients. Especially impressive was 1 patient with pulmonary vascular resistance of 8 Wood units when he was 1 month old. Two others at 7 months of age had pulmonary vascular resistance of 8 and 21 units, showing that severe resistance changes can occur very early in life.

Whether early operation would affect the natural history of obstructive pulmonary vascular disease is not known, and postoperative catheterization data such as Dr. Midgley has presented are important in understanding this complex congenital cardiac anomaly.

DR. ANTHONY R. C. DOBELL (Montreal, Que, Canada): I have enjoyed this paper very much, and I must say I cannot disagree with anything in it.

It has surprised me greatly in the past few years to come to realize that complete AV canal is an anomaly that we surgeons greatly overestimated, at least from the point of view of the difficulty of its surgical repair. It is, after all, an appalling defect with a lack of the base of the ventricular septum as well as the large atrial communication and AV valve deformities. But surgical results following repair, even in infancy, have become very respectable. The reason is, I think, that we can eliminate the large left-to-right shunt and have learned to do an adequate repair of the AV valves. I think the primary reason for heart failure in infancy is the shunt, and we have eliminated that shunt. I certainly don't believe this repair is complete but it suffices during childhood in most patients. Certainly intracardiac repair is the only operation to be considered in a patient with an AV canal without an obstruction of the pulmonary artery.

The secret of the valve repair is to suspend the central portions of the valves at the appropriate level on the patch used to close the defect. As the halves of the anterior leaflet of the mitral valve are sutured, judgment is needed to know when to stop. Dr. Doty referred to this point. Sometimes with the freefloating or type C valves untethered to the ventricular septum, I have divided the patch in half and exposed the ventricular septum and put half the patch under the valve and the other half above. In other words, I have worked in the other plane. But more often, the valves must be incised. Care is taken to make the best possible reconstruction of the mitral valve, and the tricuspid valve is repaired as well as can be with the remaining valve tissue.

My final comment is that because so many of these children have Down's syndrome, it is mandatory that a considerable amount of time be spent with the parents to explain the action that the surgeon has advised. I think we require considerable wisdom to operate on these infants who have a limited future.

DR. DONALD R. KAHN (Madison, WI): This is a superb series by Dr. Midgley. Although I don't have much to add, I will emphasize a few things.

The dramatic improvements in results with operation for AV canal came about with the technique described by Rastelli, Ongley, Kirklin, and McGoon in 1968. This is the technique we are still using.

At the University Hospital, 21 consecutive patients with AV canal have undergone repair since 1972. Eight were less than 2 years old. It has been our policy in the past three years to do repair in these patients when they are about 1 year old. We have had no operative deaths. We differ from Dr. Midgley in that we have had only 1 late death, an accident due to a head injury.

The important operative steps are to suture the mitral valve evenly, to place the sutures for the patch closure of the defect 1 cm from the edge of the right ventricle to avoid heart block, and to use most all of the common mitral and tricuspid leaflets to make up the mitral valve when needed to prevent significant mitral insufficiency. A number of patients still have mild to moderate amounts of mitral insufficiency. The valve is reattached to the patch-closed defect at its normal anatomical position to prevent any left ventricular outflow tract obstruction.

No child less than 2 years old should be considered inoperable because of too high a pulmonary vascular resistance. At this age, this measurement is not a good indicator of permanent vascular changes. I have seen several children with very reactive pulmonary arterioles in whom the pulmonary vascular resistance was calculated as very high and then dropped to almost normal immediately after repair.

DR. MIDGLEY: I thank the discussants for their comments. As regards Dr. Doty's question about pledgets and the method of repair and reconstruction of the mitral annulus, we haven't found it necessary to use the pledgeted technique in this region. This is especially true in the infant group. I find pledgets a little cumbersome and obtrusive to this area and believe they would interfere with valve mobility. To date, we have not had any valve dehiscences. The 1 patient who required valve replacement had very markedly deficient mitral apparatus for original reconstruction. Whether it is advantageous or not, I do use stretch Dacron for the prosthetic patch repair. This may give, in the immediate perioperative period, some absorption of stress forces and may have some bearing on our good results as far as the absence of mitral regurgitation is concerned.

Regarding the rolled edges, I try to evert them when possible in order to gain a bigger cross-sectional dimension of the mitral valve. Certainly, when the chordal apparatus is pulling in the other direction, this is a detrimental method, and in that instance, I close them edge to edge.

I have used left ventricular vents in all instances and feel quite strongly about them, even though 1 patient did have a small left ventricular aneurysm at the vent site. I have been able to assess mitral valve function effectively without any catheter traversing the mitral valve. In 1 patient I was able to identify a major leak at the posteromedial commissure, and a simple annuloplasty stitch in this region corrected a substantial degree of mitral regurgitation.

As regards age at operation, average age at operation in our patients has become younger as our awareness of these factors has grown.

In response to Dr. Dobell's comments, I, too, emphasize the importance of dealing with the families of patients with Down's syndrome ahead of time.

I think that resistance levels, as emphasized by Dr. Kahn, are of major importance, and I consider the lability of the resistance to be the main factor, that is, whether it is changed with oxygen and Priscoline (tolazoline). As long as lability can be demonstrated, operative candidacy is assured.

Repair of Mycotic Aneurysms of the Aorta Involving the Aortic Valve

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John V. Zeok, M.D., Joe R. Utley, M.D., Michael R. Jones, M.D.,
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ABSTRACT **This report summarizes our successful management of 6 patients who underwent repair of mycotic aneurysms of the ascending aorta within a four-year period. Repairs have been successful despite involvement of as much as two-thirds of the circumference of the aortic valve annulus, involvement of the origin of the right coronary artery, and development of heart block. Three patients required surgical intervention because of hemodynamic decompensation before they had completed antibiotic therapy for endocarditis.**

In 3 patients, the aneurysm was buttressed with the valve skirt so that aneurysm repair and valve replacement were accomplished in continuity. In 2 patients, the aneurysm was repaired separately and the valve seated on the repair. In 1 patient, a large defect between the left and right coronary arteries was repaired with a woven Dacron patch secured to the valve skirt. The valve was seated to the left ventricle and the graft to the aorta. There were no operative or postoperative deaths. Our data suggest that mycotic aneurysms of the aortic annulus can be successfully repaired despite extensive damage.

Despite the introduction of effective antimicrobial therapy, the mortality from bacterial endocarditis has remained between 15 and 50% [3, 5]. The majority of deaths occur because of congestive heart failure [4, 5, 9, 11]. Surgical management of patients with severe progressive congestive heart failure prior to completion of standard antimicrobial therapy has been advocated by many [3–6, 9, 12–15].

The advent of more aggressive surgical management has made the discovery of mycotic aneurysms of the aortic valve annulus more frequent [1, 10]. These lesions are particularly challenging to the surgeon because destruction of the aortic annulus produces loss of continuity between the aorta and the left ventricular musculature. This report summarizes the experience at the University of Kentucky Medical Center during a four-year period with surgical repair of 6 patients with mycotic aneurysms originating from the aortic valve.

Material and Methods

From August, 1975, to August, 1979, 6 consecutive patients underwent operation at the University of Kentucky Medical Center Hospital for repair of mycotic aneurysms of the annulus of the aortic valve. Clinical data are summarized in the Table. The patients ranged from 18 to 60 years old. Five were men and 1 was a woman. Four patients required operation for congestive heart failure; 1 for cardiac tamponade secondary to rupture of the aneurysm; and 1 for recurrent paravalvular leak after aortic valve replacement. Three patients required surgical therapy for hemodynamic deterioration prior to completion of antibiotic therapy for bacterial endocarditis.

The extent of disease involvement and its location are characterized in Figure 1. In all patients, there was destruction of the annulus of the aortic valve to a variable degree. The most extensive destruction, depicted in Figure 1E, involved two-thirds of the circumference of the annulus, produced heart block, and involved the right coronary artery ostia. All the male patients had congenital bicuspid aortic valves. The female patient was thought to have rheumatic valvulitis.

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Indication for Surgical Management

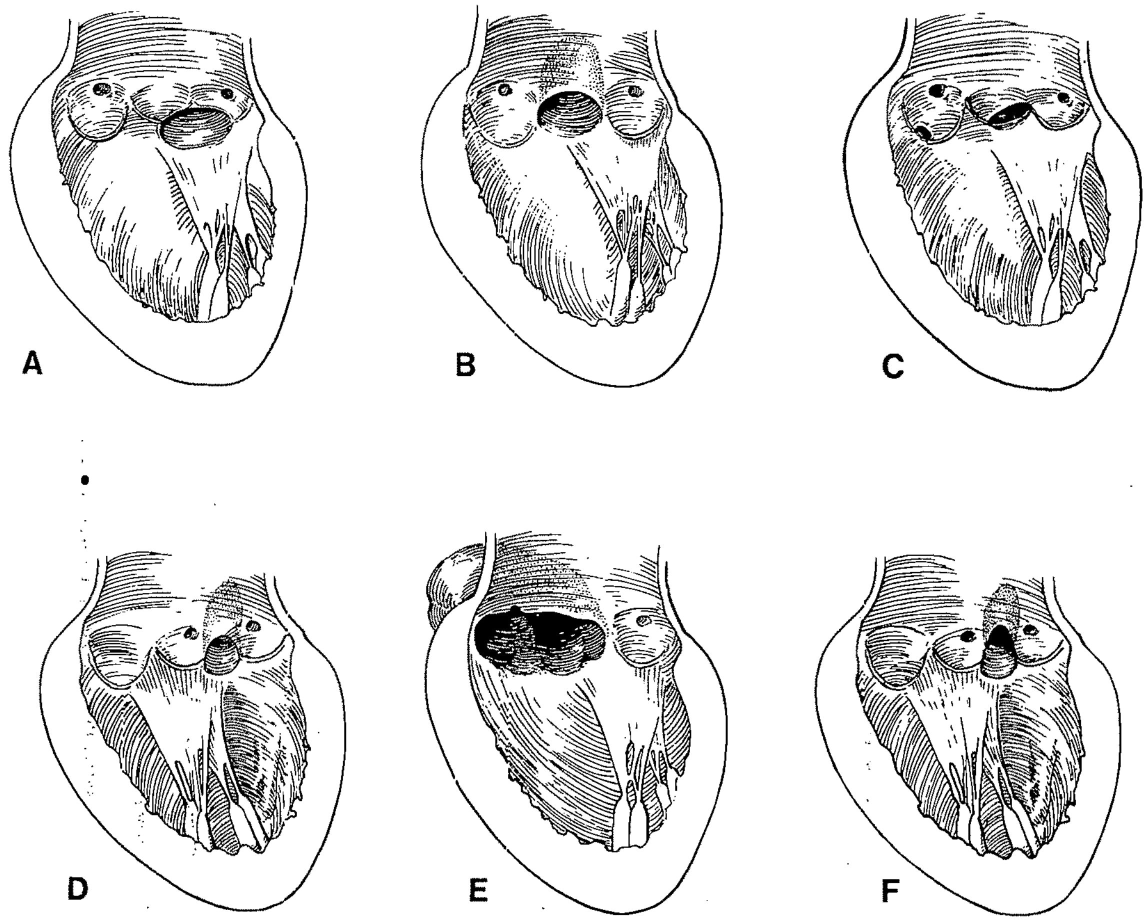
Patient No., Age (yr), Sex	Indication
1. 22, F	Paravalvular leak, hemolysis, CHF
2. 18, M	CHF
3. 21, M	CHF, emboli
4. 56, M	CHF
5. 60, M	Cardiac tamponade
6. 43, M	CHF

CHF = congestive heart failure.

We used three types of surgical repairs (Fig 2). In the repair shown in 2A, the aneurysm is closed primarily with buttressed mattress sutures, and the valve is secured to the repair. Two patients were repaired with this technique (see Fig 1A,B). In the repair depicted in Figure 2B, the aneurysm sutures are buttressed on one side with Teflon felt and on the other with the valve skirt, so that the aneurysm repair and valve replacement are accomplished in continuity. Three patients were repaired with this technique (see Fig 1C, D, E). The patient with the disease involvement in Figure 1E also required a right coronary artery bypass and a permanent pacemaker for complete heart block.

In the last patient (see Fig 1F), the aortic destruction was so extensive that any attempt to use the repair in A or B of Figure 2 would have produced occlusion of both the right and left coronary artery orifices. Therefore the repair characterized in Figure 2C was used. An appropriately sized segment of woven Dacron graft was sutured to the skirt of a Björk-Shiley aortic valve prosthesis. The valve was secured to the ventricular musculature at the base of the defect with heavy Teflon felt buttressed mattress sutures. Smaller mattress sutures were used to attach the patch to the aorta. The valve seated well but, despite the efforts to avoid injury to the coronary arteries, it appeared at the completion of this repair that the right coronary

Fig 1. Extent of disease involvement and its location in the 6 patients.



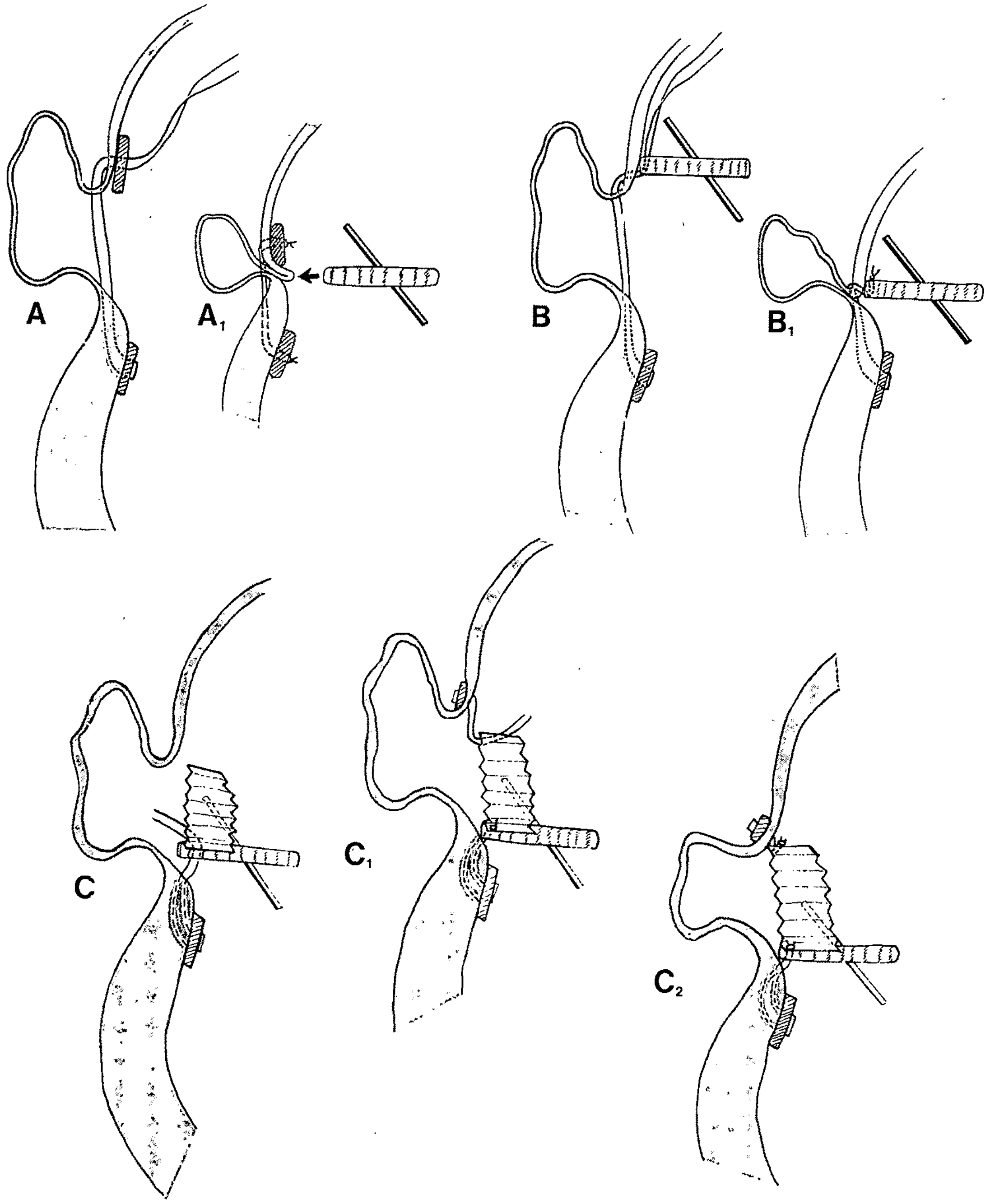


Fig 2. Types of surgical repair. See text for details.

orifice was constricted. A single reversed saphenous vein bypass was carried out to the distal right coronary artery.

In every repair reported here, the Björk-Shiley prosthesis was used. The major commissure was pointed toward the repair so that the buttressed sutures in the left ventricular musculature would not interfere with valve mobility.

Results

All 6 patients are alive and available for follow-up twelve to fifty months after surgical repair. All are on a regimen of anticoagulants and are well compensated without evidence of recurrent aneurysms or paravalvular leak. In 3, angiography confirmed completeness of repair.

Comment

The surgical approach to mycotic aneurysms of the annulus of the aortic valve has not been established. Buckley and colleagues [1] suggested extensive resection of all involved tissue for control of infection in patients with bacterial endocarditis. However, the location of the aneurysms makes anything other than aortic valve resection and internal debridement of the aneurysm impractical. True resection of all affected tissue could make satisfactory repair impossible.

In the series reported here, no attempt was made to resect the aneurysms. The valve was excised and the aneurysm debrided from inside the aorta. In the 3 patients who underwent emergency operation, bacteria were identified either in the resected valve or in purulent fluid drained at operation from the valve annulus, but cultures of the tissue and fluid were sterile. There were no recurrent infections on the implanted prosthesis. Infection was controlled by preoperative and postoperative antibiotics.

Several investigators [1, 7, 8] have advocated buttressed suture techniques similar to those represented in A and B of Figure 2 and used in 5 of the 6 patients reported here. To our knowledge, the type of repair characterized in 2C has not been reported previously. In the other techniques presented here the tissues are pulled together in order to close the defect in the aorta produced by the infectious process. If the tissue comes together readily, no problem should arise. If the defect is large, the tension required to pull the tissues together will be similarly increased, and subsequent breakdown of the repair is more likely. These considerations suggest superiority for the technique in which the defect is repaired with graft material attached to the valve. In the area of the aneurysm, the valve is seated firmly on the ventricular musculature and the graft is utilized to repair the defect in the aorta. Tension should be minimal.

Several previous investigators [2, 4] noted the proximity of the defects to the coronary arteries and the difficulty in obtaining a satisfactory repair without affecting coronary flow. The approach used in our patients was to sacrifice the coronary artery orifice, when necessary, to assure a secure closure of the aneurysm. With this approach, coronary artery bypass was required in 2 patients.

It has been suggested that success should not be expected when aneurysms are extensive [8, 12]. Our results, however, indicate that available techniques allow mycotic aneurysms of the aortic annulus to be repaired successfully despite extensive associated damage.

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Long-Term Follow-up of the Björk-Shiley Prosthetic Valve Used in the Mitral Position

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ABSTRACT **This study analyzes 547 patients who had mitral valve replacement with a Björk-Shiley prosthesis over a 9-year period (mean follow-up, 46.5 months). Operative mortality was 7.3%, and 5-year survival was 76.9%. Serious anticoagulation problems occurred in 1.8% (10 patients) and serious thromboembolic episodes in 5.3% (28 patients) (1.3 per 1,000 patient-months). The study includes 257 patients with isolated mitral valve replacement (Group 1) and 290 who had associated procedures (Groups 2 through 5). Hospital mortality in Group 1 was 2.7% compared with 11.7% in Groups 2 through 5 ($p < 0.01$). Five-year survival for Group 1 was 83.9% and for the others, 70.5% ($p < 0.01$), and two-thirds of the deaths occurred in Groups 2 through 5.**

In the patients in Group 1 with pure mitral insufficiency (MI), 5-year survival was 70.9%, significantly lower ($p < 0.05$) than the 90.2% for those with pure mitral stenosis (MS) and 84.3% for those with combined stenosis and insufficiency (MI + MS). In Groups 2 through 5, 5-year survivals were 56.0% (MI), 82.5% (MS), and 71.4% (MI + MS).

Significantly lower ($p < 0.01$) 5-year survival was found for those in Functional Class IV preoperatively compared with Class III or II. In Group 1, 89.1% were in Class II, 86.7% in Class III, and 64.8% in Class IV. The corresponding figures in the combined other groups were 72.7%, 76.4%, and 48.9%, respectively. This study shows that rhythm plays a small role in thromboembolic episodes and survival and that there is strong evidence for early operation in patients with MI.

In the past 10 years we have performed valve replacement in approximately 1,300 patients with the Björk-Shiley prosthesis. This study relates our experience with 547 patients who underwent mitral valve replacement with this prosthesis in the 9 years from January 1, 1970, through December 31, 1978. All patients who underwent associated procedures or had had previous cardiac operation were included. The mean follow-up was 46.5 months.

Material and Methods

Patients were divided into five groups according to the procedure done (Table 1). Group 1, 257 patients, had isolated mitral valve disease and no associated procedure. Group 2, 53 patients, had mitral valve replacement and coronary bypass operation. Group 3, 82 patients, had both mitral and aortic valve replacement. Group 4, 48 patients, had mitral valve replacement and other associated cardiac and great vessel procedures, such as resection of the aorta and aortic valve replacement or resection of a left ventricular aneurysm. Group 5, 107 patients, had had at least one previous operative procedure for valve disease—be it commissurotomy, annuloplasty, or valve replacement.

Patients ranged from 10 to 76 years old (mean age, 54 years). Those who had bypass were significantly older ($p < 0.05$) with a mean of 60.3 years than the other four groups (see Table 1).

Patients were also divided into subgroups by preoperative New York Heart Association (NYHA) Functional Class and by the nature of the lesion of the mitral valve: mitral insufficiency (MI), mitral stenosis (MS), or mixed mitral insufficiency and mitral stenosis (MI + MS) (Table 2).

Patients were followed by yearly office visits and a mail survey. Those who did not respond were reached by telephone or located through their cardiologist, family physician, or relative. All data were computer analyzed. Eight patients were lost to follow-up; overall follow-up was 98.5%. The study focused on the patient's

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Table 1. Patient Profile of 547 Patients Divided according to Procedure Performed

Group	Procedure Done	No. of Patients	Mean Age (yr)	Operative Mortality (%)
1	Isolated MVR	257	51.7	2.7
2	MVR + bypass	53	60.3	5.7
3	MVR + AVR	82	52.7	12.2
4	MVR + misc.	48	54.0	18.7
5	MVR + previous	107	49.6	10.3

MVR = mitral valve replacement; AVR = aortic valve replacement.

Table 2. Patient Profile of 547 Patients according to Pathophysiology and Preoperative Functional Class

Variable	No. of Patients	Mean Age (yr)	Operative Mortality (%)
Pathophysiology			
MS	163	51.4	4.9
MI	134	55.4	9.7
MS + MI	250	51.5	7.6
Preop NYHA Functional Class			
II	135	50.8	5.2
III	317	53.0	5.7
IV	95	52.9	15.6

MS = mitral stenosis; MI = mitral insufficiency; NYHA = New York Heart Association.

Functional Classification, quality of life, thromboembolic complications of the valve or anticoagulants or both, and long-term survival determined by actuarial curves. Although 7-year survival can be determined in this 9-year study, numbers at risk after dividing the patients into groups were small and we elected to look at 5-year survival only.

The method of surgical management of these patients has been described previously [1, 6]. A bubble oxygenator and a roller pump with moderate hypothermia (30°C) and hemodilution were used in all patients. Valves were inserted by means of interrupted mattress sutures with pledgets of Teflon felt as a buttress. Perfusion of the coronary arteries was used early; later, deep regional cardiac hypothermia utilizing electrolyte solution at 4°C in the pericardium and intracavitary hypothermia of the left ventricle were used for myocardial protection in all aortic and double-valve replacements. In the latter procedures, the mitral valve was resected, and all sutures were placed through the annulus and subsequently through the prosthesis; the valve was then laid aside and the complete aortic valve replacement was performed so as to reduce clamp time. The mitral valve was tied into place after the aortic clamp was released.

All patients were extensively monitored in the intensive care unit, and usually transferred to the floor in 48 hours. Anticoagulation with intravenously administered heparin was carried out soon after removal of the chest tubes on the day following operation. Heparin was given on a 4- to 6-hour basis, depending on the Lee-White clotting time. Warfarin was begun as soon as the patient could take liquids orally, and a goal of 20 to 30% of normal (therapeutic range) was sought. Heparin was administered for a full 7 days, even though a therapeutic range of warfarin had been achieved earlier. Patients were usually discharged from the hospital 8 to 10 days postoperatively. Personal follow-up was carried out by the surgeon and the cardiologist in most instances, and tight anticoagulant control was attempted.

Results

Surgical

Forty (7.3%) of the 547 patients did not survive the operative period (30 days) (Table 3). The surgical mortality ranged from 2.7% (7 patients) in Group 1 (valve replacement only) to 18.7% (9 patients) in Group 4 (replacement and other procedures) (Fig 1; see Table 1). Complications in the postoperative period included postoperative bleeding for which a moderate number of patients were returned to the operating room, and occasional late tamponade. The balloon pump assist was used in only 7 patients, with 4 survivors. Inotropic and chronotropic drugs along with digitalis and diuretics were used more often, and hypertension,

Table 3. Total Mortality in 9-Year Study

Cause of Death	30 Day	Late	All
Congestive heart failure	9	23	32
Myocardial infarct	9	10	19
Arrhythmia	3	9	12
Stroke	5	7	12
Cardiac arrest	2	8	10
Infection	2	6	8
Bleeding	4	0	4
Valve malfunction	1	3	4
Low cardiac output	1	0	1
Other heart-related	4	2	6
Other not heart-related	0	12	12
Total	40	80	120

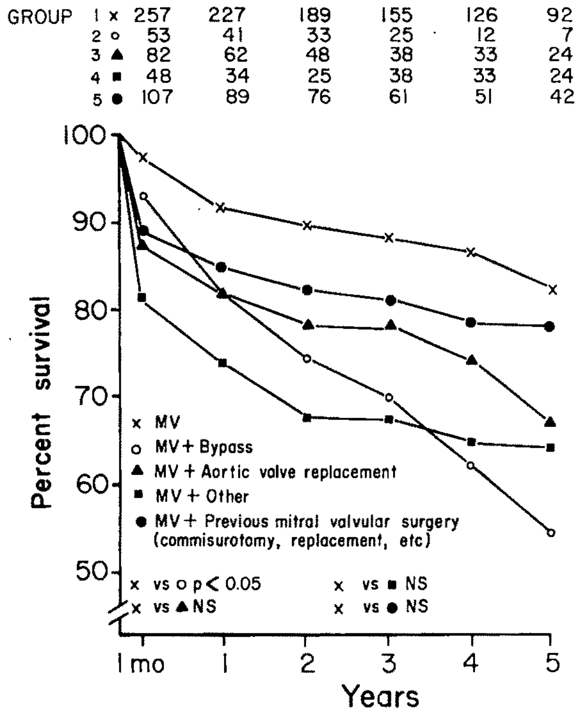


Fig 1. Operative and long-term survival of the five groups having mitral valve (MV) *replacement. Note the MV + bypass group has the greatest mortality, but no other statistical significance exists between the MV group and the others. Numbers across the top represent the number of patients at risk in each time period.* (NS *= not statistically significant.)*

when present, was controlled by drugs. The operative mortality appears comparable to other series [2, 3, 8].

Functional

Figure 2 shows the number of patients who were improved, unchanged, or worse. Relatively few remained in Class III or IV. Overall, of those currently alive, 82% (343) have improved at least one NYHA Functional Class, and 42% (176) reported on our survey that they were asymptomatic. Drug therapy was continued in large numbers: 353 reported they were taking digitalis and 159, diuretics.

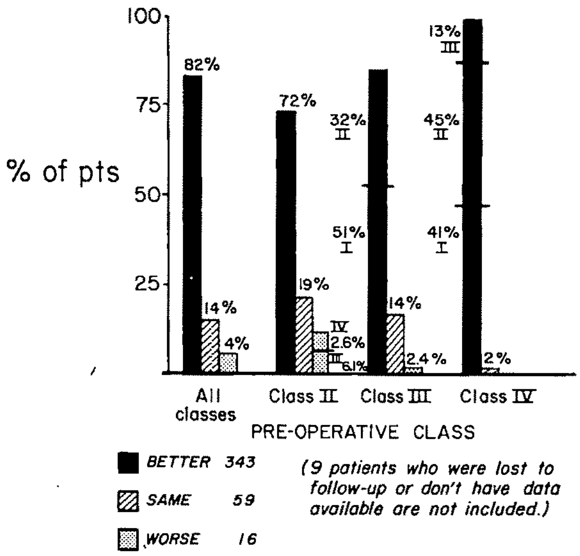


Fig 2. Change in preoperative to postoperative New York Heart Association Functional Class in late follow-up. All but 75 patients improved.

Complications

THROMBOEMBOLIC EPISODES. Forty-nine patients sustained 62 emboli. Three patients refused to take Coumadin (sodium warfarin). One of them had 5 emboli in a year, another had 4 in a year, and another had 2 in a year, the second being fatal. Twenty-eight patients had residual effects, which resulted in 18 deaths. In some of these patients a clotted valve or embolization was a contributing cause of death. Excluding those who stopped Coumadin and considering only serious and fatal emboli, there were 28 emboli per 22,230 patient-months or 1.3 per 1,000 patient-months (1.6 per 100 patient-years). This compares favorably with other reported series [5, 7, 8, 10]. Another 33 patients had only transitory effects that possibly were not due to emboli but were considered to be embolic due to their questionable nature. All episodes were carefully traced. Any episode reported in the questionnaire, but not recorded in hospital records, was verified with the patient's personal physician or cardiologist. If the 3 patients who stopped Coumadin are excluded, there were a total of 46 patients who had 51 emboli, with or without residuals, an overall incidence of 2.3 per 1,000 patient-months.

ANTICOAGULATION. Ten patients (1.8%) have reported major bleeding problems requiring hospitalization during the 9-year study. Location of bleeding was renal in 3, gastrointestinal in 3, subdural hematoma in 2, eye in 1, and uterine in 1. None of these patients died and none have experienced residuals except partial blindness in the patient with retinal hemorrhage. Numerous other patients reported nose bleeds, metrorrhagia, and bruises, which were extremely difficult to evaluate.

VALVE MALFUNCTION. Three patients died of thrombotic obstruction of the valve, and since they were remote from definitive care or since the problem was not recognized, no surgical attempts were made. In another, cause of death was thought to be due to the mitral prosthesis obstructing the outflow tract of the left ventricle. Other than the three clotted valves, this represents the only malfunction of the valve in the entire series. Paraprosthetic leaks requiring surgical repair were three in number, all following bacterial endocarditis successfully treated medically.

INFECTION. Bacterial endocarditis developed in 12 patients (2.2%). Eight of these 12 died, 2 in whom it developed early and 6 in whom the infection developed late. The most common organism was *Staphylococcus epidermidis*, and most patients sought medical treatment late. The 4 survivors were seen early and were operated on in the face of infection and hemodynamic failure or had repair after infection was controlled. The 8 patients who died, including 4 with resistant hemolytic *S. aureus* were treated late.

Mortality

To date there have been 120 deaths. Overall operative mortality (within 30 days) was 40 (7.3%). Late mortality occurred in 80 patients (14.6%). Table 3 lists the cause of death. Of the patients who died late, 11 were in preoperative Functional Class II, 44 in Class III, and 25 were in Class IV.

Survival

Five-year survival and operative mortality varied with the type of procedure done, preoperative NYHA Functional Class, and the nature of the lesion. Overall 7-year survival is 70.9% (Fig 3). For those patients who had mitral valve replacement only, surgical mortality was 2.7%, comparable with other reports (see Fig 1). MI was associated with a higher operative mortality (5.3%) than either MS (2.4%) or mixed MI + MS (1.7%) (Fig 4B). Five-year survival in those with isolated MV was 83.9% (see Fig 1), but in this group, survival of patients with MS was 90.2% whereas with MI it was only 70.9% ($p < 0.05$) (see Fig 4B).

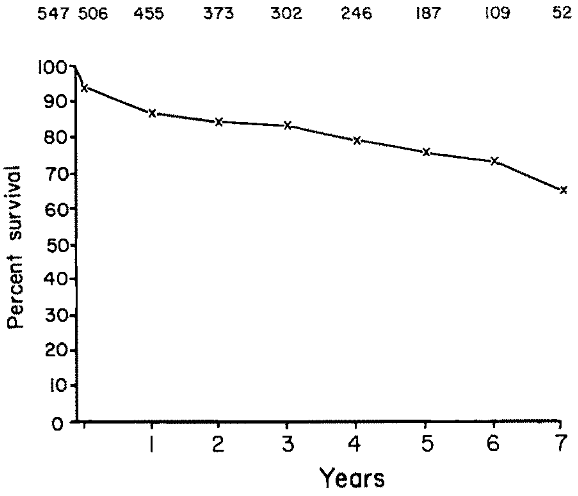
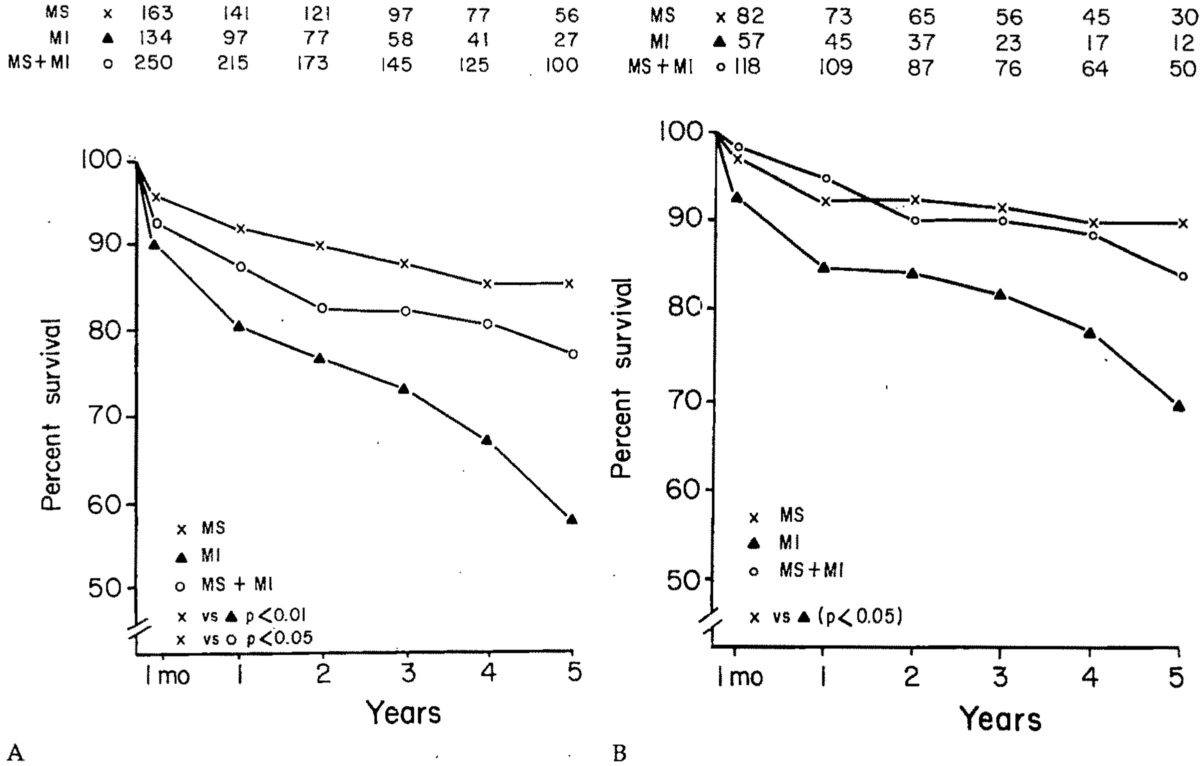


Fig 3. Survival among 547 patients 7 years after replacement of the mitral valve.

For those patients who had associated procedures done, operative mortality was significantly higher—11.2% ($p < 0.01$)—compared with Group 1, and 5-year survival was significantly lower—70.5% ($p < 0.01$). Figure 4 depicts the overall actuarial survival curve, according to the procedure performed and by pathophysiology, again showing a striking difference between patients with MS and those with MI ($p < 0.01$).

Operative mortality for those in NYHA Class IV was considerably higher than for those in Classes II and III. In the overall group, 5-year survival was lower for those in Class IV, 56%, than in Class II, 84%, or III, 82% ($p < 0.01$) (Fig 5A).

In analyzing the life-table survival curves of those who were in atrial fibrillation or sinus rhythm preoperatively or postoperatively, there



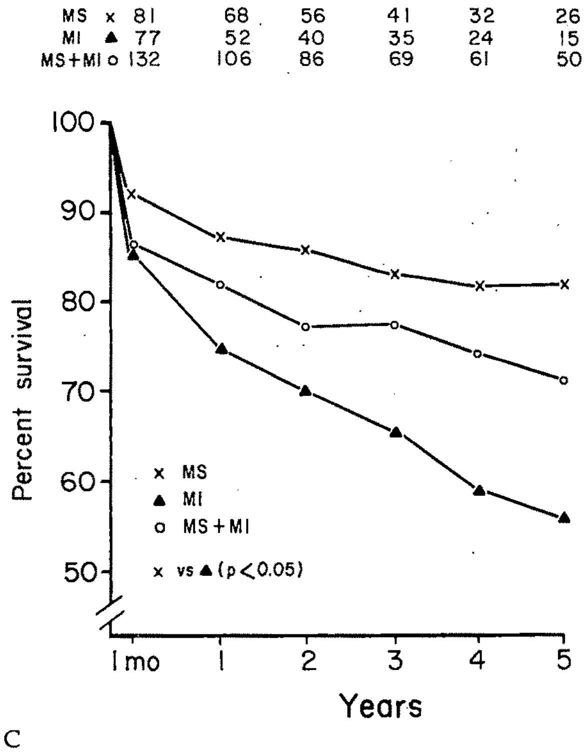
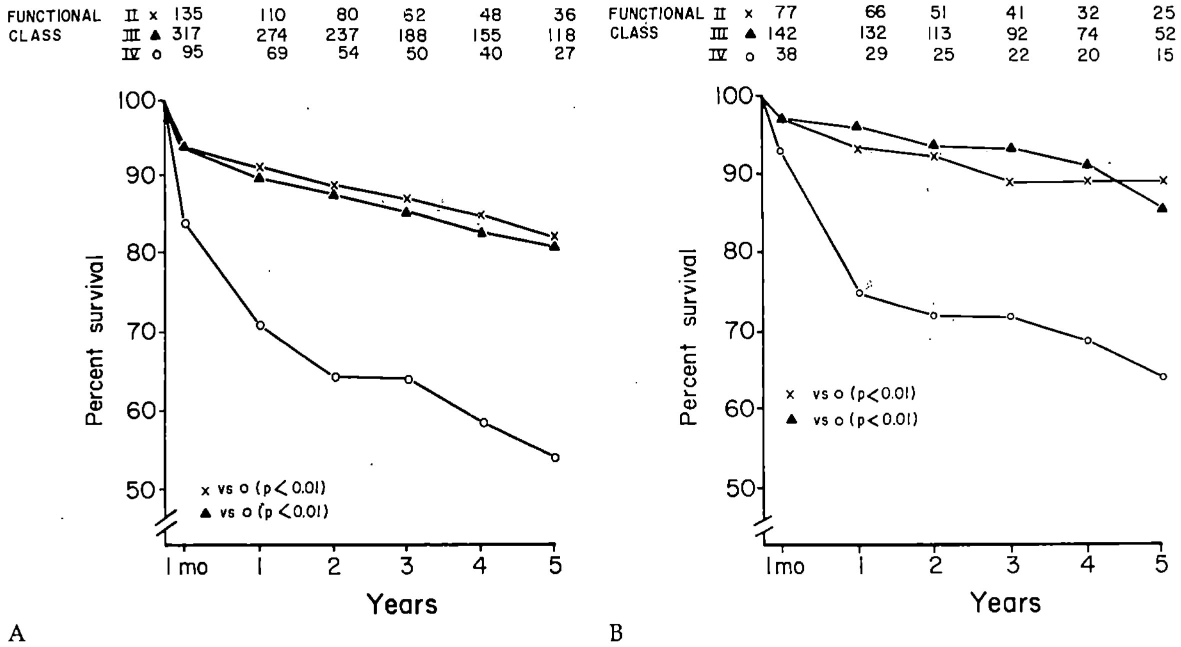


Fig 4. A comparison of 5-year survival by pathophysiology. (A) Overall survival, (B) survival in Group 1, and (C) survival in Groups 2 through 5. Note the consistency of significant difference in survival in all three. Numbers across the top represent the number of patients at risk in each time period. (*MS = mitral stenosis; MI = mitral insufficiency.*)

was no significant difference in long-term survival (Fig 6). Calculation of the incidence of thromboembolism in patients with atrial fibrillation or sinus rhythm also shows no statistical difference. These findings apply to the overall group, Group 1 and Groups 2 through 5.

Comment

This study shows strong evidence for the left ventricle being "at risk" in MI. The left ventricle hypertrophies and dilates in an effort to compensate for the regurgitation. As the ventricle becomes increasingly overloaded, irreversible damage due to insidious, diffuse fibrosis occurs, and merely putting a competent valve in the atrioventricular orifice will not restore the lost left ventricular function. By comparison, in patients with MS the stenotic valve protects the left ventricle from becoming overloaded so they lose relatively little, if any, left ventricular function. In the overall group of 547 patients (see Fig 4A), a lesion of MI was associated with an operative mortality of 9.7%, which is significantly higher than the 4.9% for MS ($p < 0.01$) and higher than 7.6% for MI+MS. Five-year survival was significantly lower for those patients with MI, 60.7%, than MS, 86.5%



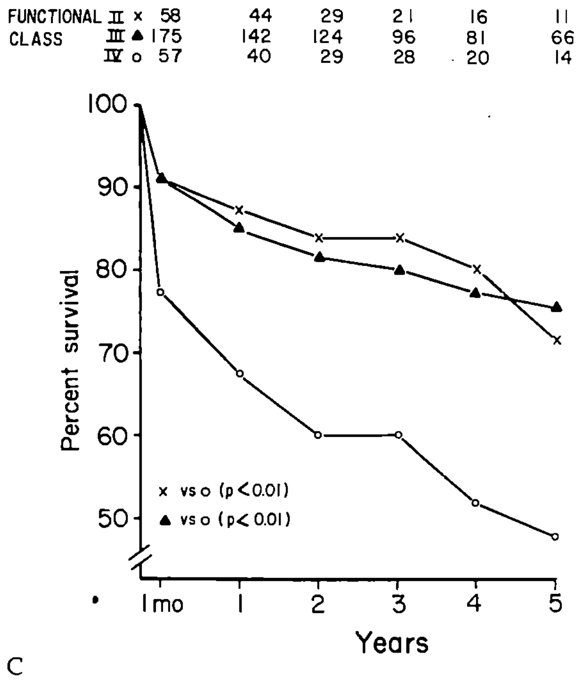
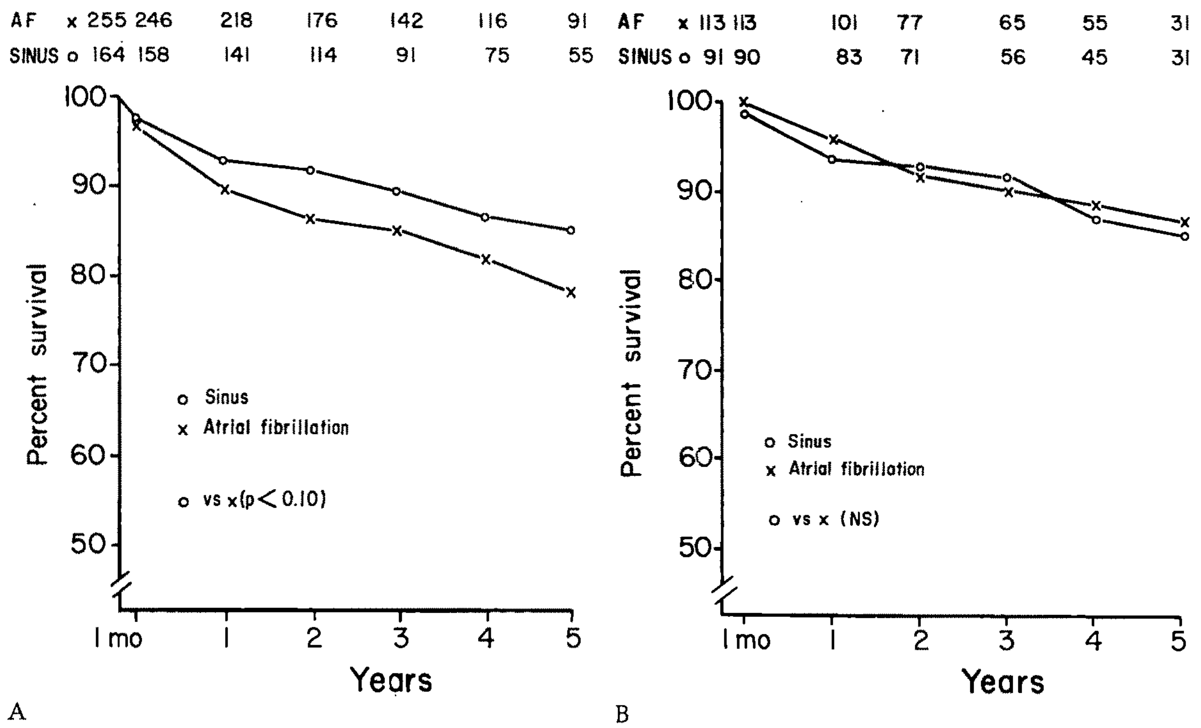


Fig 5. Survival by preoperative New York Heart Association Functional Class (A) overall, (B) in Group 1, and (C) in Groups 2 through 5. Note the significant difference in survival between Functional Classes II and III compared with IV. Numbers across the top represent the number of patients at risk in each time period.

($p < 0.01$) and those with MI+MS than MS ($p < 0.05$) (see Fig 4A).

An analysis of symptom duration shows a median of 12 months in MI, whereas the median for symptoms in MS was 36 months prior to operation ($p < 0.01$). Patients with MI (22%) achieved the Functional Class IV level much sooner, and in terms of percentages, there are more of them than those with MS (11%). In looking at operative mortality and 5-year survival, we find a statistically significant difference between Class II and Class III in the two lesions ($p < 0.01$). Since the only variable not present in those patients with pure MS is overwork of the left ventricle, we must conclude that the left ventricle in patients with MI is in jeopardy at the onset of regurgitation. Since the surgical risk in Group 1 patients with MI is 5.3% compared with 2.4% for those with MS and since only a 70.9% 5-year survival was achieved for Group 1 patients with MI compared with 90% for those with MS ($p < 0.05$), it would appear that earlier operation should be carried out (see Fig 4B). Possibly the use of repeated echo studies to determine dilatation and wall thickness, and gated nuclear studies to evaluate ejection fraction and contractility at rest and exercise should be used as criteria for operative intervention rather than symptoms.

Neither the preoperative rhythm nor the



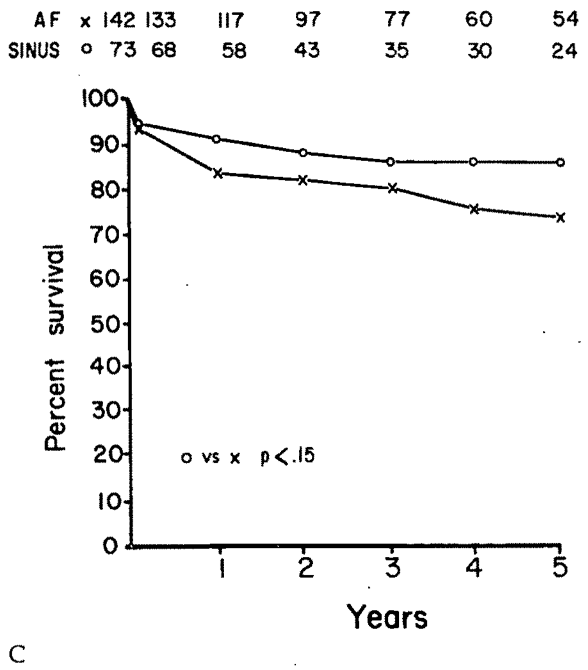


Fig 6. Analysis of postoperative rhythm in relation to survival (A) overall, (B) in Group 1, and (C) in Groups 2 through 5. No significance can be found except at the 10 to 15% level. Numbers across the top represent the number of patients at risk in each time period. (AF = *atrial fibrillation.)*

rhythm at the time of discharge from the hospital was a significant factor in the occurrence of thromboemboli. Patients were converted to sinus rhythm before leaving the hospital, if possible, and very few were converted late (see Fig 6).

Since statistical significance had been achieved in looking at several risk factors, all of these were weighed with reference to their priority as determinants for outcome using Cox' regression analysis [4]. Table 4 was thus constructed. Four variables were found to be most important. These are in regression of importance: age ($p < 0.001$), Functional Class ($p < 0.001$), group ($p < 0.01$), and MS versus MI ($p < 0.05$). Using this table, a good prediction for 5-year survival can be readily achieved.

We have presented a statistical analysis of the early and late results of mitral valve replacement using one prosthesis. A breakdown of the patients having only mitral valve replacement and those having additional procedures has allowed a thorough analysis.

Surgical mortality and complications of embolization and bleeding due to long-term anticoagulants have been reasonable. Surprisingly, there appeared to be no statistical correlation between cardiac rhythm and embolization or

Table 4. Probability of 5-Year Survival according to Regression Analysis of Four Most Important Risk Factors

Age (yr)	Operative Class	Functional Class II or III[a]		Functional Class IV[a]	
		MS	MI	MS	MI
60	MVR	87	79	74	57
	MVR + other	78	65	60	39
50	MVR	92	86	82	72
	MVR + other	85	76	62	54
40	MVR	94	91	88	79
	MVR + other	90	83	81	67

[a] Numbers in the columns represent percentages.

MS = mitral stenosis; MI = mitral insufficiency; MVR = mitral valve replacement.

long-term survival. This suggests a need for reconsideration of the use of cardioversion postoperatively.

The long-term results of surgical intervention in patients with MI are poor regardless of the degree of symptomatology or hemodynamic change at the time of operation. Since the only variable not found in patients with MS (in whom excellent results were achieved) is the overloaded left ventricle, it would appear that much earlier intervention must be carried out.

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Discussion

DR. ROBERT B. KARP (Birmingham, AL): I complement Dr. Lepley and his associates on such a thorough analysis of a large group of patients having mitral valve replacement. Among the group of 741 patients who had Björk-Shiley valve replacement at the University of Alabama at Birmingham and recently were analyzed, there were 191 who had mitral valve replacements. Hospital mortality was similar to that of Dr. Lepley's group, and the trend in hospital mortality was higher among patients with mitral regurgitation than in patients with mixed lesions or mitral stenosis. However, recently there has not been such a prominent difference.

One begins an analysis of valve replacement to characterize device performance, and long-term survival may, in part, reflect valve performance. However, Dr. Lepley has called to our attention other very important factors, apparently independent of the device, that affect late survival. Certainly mitral incompetence did have an effect in his series.

Using a similar Cox regression for all patients with implantation of a Björk-Shiley valve, we at the University of Alabama found that several other preoperative and intraoperative factors altered prospects for long-term survival. However, the specific valve lesion was not among them. Certainly, previous valve replacement, Functional Class, and double-valve replacement are factors common to our series and that of Dr. Lepley's group. In addition, for all patients we noted that duration of intraoperative ischemia time and ventricular arrhythmias occurring near discharge decreased late survival.

The steepest downward slope in late survival for Dr. Lepley's series is for patients having mitral valve replacement and coronary artery bypass grafting. Our Björk-Shiley series did not reflect that trend. However, that effect was seen in our analysis of patients having the porcine bioprosthesis in the mitral area. The discrepancy might be due to selection of a porcine bioprosthesis in patients with ischemic mitral valve disease—the correlation thus occurring between poor survival and ischemic cardiomyopathy. I wonder if in the patients with mitral regurgitation, Dr. Lepley has broken down the etiology of the mitral regurgitation to be either ischemic or rheumatic.

In the present series, Dr. Lepley's group showed improvement in Functional Class to be quite good; 82% improved by at least one Functional Class. But I gather that figure is a proportion of live patients. Our series showed similar improvement; 77% of Class III and 72% of Class IV patients improved at least one class. However, 9% and 28% of Class III and Class IV patients, respectively, died. This simply serves to reinforce the attitude that earlier operation is needed in some patients who are in Class III or IV.

In general, the incidence of late valve thrombosis in the University of Alabama series was perhaps two to four times that of Dr. Lepley's series. Would he suggest that this is because we did not use a regimen of heparin in the early postoperative hospital course?

DR. LEPLEY: I thank Dr. Karp for his kind comments. Concerning the relationship of mitral insufficiency to coronary ischemia, you notice that we separated out the groups that had an additional procedure performed. It is hard to evaluate mitral valve replacement if a triple vein bypass is combined with that operation. In such a series, evaluation as far as a "pure" group is concerned becomes impossible.

I doubt that ischemia was a factor. For the most part, at our institution we do mitral valve replacement with the patient under deep local hypothermia and with about twenty minutes of clamp time because we only place the pledgeted sutures through the annulus and the valve, then release the aorta while we tie the valve down. Therefore, I do not believe that myocardial ischemia was a problem in this series.

As for early anticoagulation, I have for years been an advocate of heparinizing the patient the day following operation after the chest tubes have been removed. Then we give heparin every 4 to 6 hours, to keep the partial thromboplastin time above the baseline at all times, for at least 7 days. We start the patient on a regimen of Coumadin (sodium warfarin) as soon as he can take oral liquids and have it in a therapeutic range by the time of discharge at 7 to 10 days.

Notice from the American Board of Thoracic Surgery

The American Board of Thoracic Surgery now requires that candidates pass both the written and oral portions of the certifying examination.

In 1980 and thereafter, a written examination will be given *prior* to the oral examination. It will be necessary to pass the written examination before the oral examination can be taken. The closing date for registration for 1981 was August 1, 1980. The exact times and places of these examinations will be announced later.

A candidate applying for admission to the 1981 certifying examination must fulfill all the requirements for the Board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, 14640 E Seven Mile Road, Detroit, MI 48205.

Heterograft Cardiac Valve Prostheses: A Five-Year Follow-up

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Amrit Dajee, M.D., and Edward J. Hurley, M.D.

ABSTRACT **The major advance in the management of valvular heart disease over the past twenty years has been due to prosthetic valve operation. The bioprostheses have good hemodynamic function and a low rate of thromboembolism although the long-term durability is unknown. In this series of 25 patients with 27 valves implanted over five years, there was an 8% early mortality and a 12% late mortality. There have been no thromboembolic episodes. Primary valvular dysfunction requiring operation occurred in 7.4% (2 out of 27). All surviving patients are in New York Heart Association Functional Class I or II.**

During the past twenty years various prosthetic valves have made possible major advances in the surgical management of valvular heart disease. Almost 20,000 cardiac valve prostheses are implanted in patients in the United States each year [20], and they allow the patients so treated to lead more active and useful lives. Cardiac valve operation is not without risks and serious complications during and after operation and must be balanced against the risks and complications of the natural history of the valvular heart disease.

All tissue valves simulate the flow characteristics of a natural cardiac valve. However, following the successful implantation of a heterograft prosthesis in 1965 [2], an unacceptably high failure rate was noted secondary to degeneration, fibrosis, or calcification. Most of these valves were treated with formalin, irradiation, or mercury salt solutions. The heterograft prosthesis, while having good hemodynamic function and a low incidence of thromboembolism, lacked long-term durability until glutaraldehyde preservation was introduced by Carpentier and co-workers in 1968 [6]. The tissue-compatible inert collagen polymer formed by glutaraldehyde preservation has achieved excellent pliability and durability as modified by Hancock Laboratories [19].

The noticeable improvement in clinical preservation of the heterograft valve was followed by the development of the flexible mounting stent in 1970. The flexible stent reduces tissue tension at valve closure by 90% due to inward flexion of the commissures [12]. The combination of flow characteristics of the natural cardiac valve and the durability and host compatibility of the glutaraldehyde-preserved, flexible-stented heterograft aortic valve has made this the prosthesis of choice in valvular heart operations.

The functional and hemodynamic results, initial hospital mortality, long-term survival, and valve-related complications for heterograft prostheses implanted over five years at this medical center were reviewed.

Material and Method

For this analysis, 25 patients who underwent aortic valve replacement or mitral valve replacement or both prior to January, 1975, were included. Patients who had concomitant coronary revascularization or ventricular aneurysmectomy were included. Heterograft valve replacement was carried out in all patients undergoing valve replacement during the evaluation period. Expected longevity, need for anticoagulation, and concomitant disease state did not influence the choice of the valve prosthesis. The annulus diameters of the prostheses are given in Table 1.

Standard cardiac surgical techniques for cardiopulmonary bypass utilizing a bubble-type oxygenator were employed. All procedures were performed through a median sternotomy incision with cross-clamping of the aorta. Myo-

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Table 1. Sizes of Bioprostheses

Operation	Annulus Diameter (mm)	No. of Patients
Aortic valve replacement	19	7
	21	1
	23	6
	25	2
	27	2
Mitral valve replacement	27	1
	29	3
	31	2
	33	3

Table 2. Early Mortality[a]

Operation	Total No.	Deaths	Mortality (%)
AVR	16	1	6.25
MVR	7	1	14.03
AVR + MVR	2	0	0

[a] Death of patients before hospital discharge: 1 patient who had AVR died forty-one days and 1 with MVR three days postoperatively.

AVR = aortic valve replacement; MVR = mitral valve replacement.

Table 3. Late Survival (Operative Survivors)[a]

Operation	Total No.	Deaths	Survival (%)
AVR	16 (15)	2 (1)	87.5 (93.3)
MVR	7 (6)	2 (1)	71.4 (83.3)
AVR + MVR	2 (2)	1 (1)	50 (50)

[a] Late survival includes early postoperative deaths. One patient who had AVR and 1 with MVR died late after reoperation. The patient who had AVR + MVR died out of hospital of undetermined cause.

AVR = aortic valve replacement; MVR = mitral valve replacement.

cardial preservation during periods of aortic cross-clamping was achieved by continuous irrigation of the pericardial cavity and intermittent lavage of the left ventricle with saline solution at 4°C.

Postoperatively, all patients received oral anticoagulation with warfarin sodium in standard fashion for eight weeks. Anticoagulation was then discontinued in all patients irrespective of valve or valves replaced, cardiac rhythm, or the presence or absence of intracardiac thrombi at the time of valve replacement operation.

Follow-up evaluation of all surviving patients was obtained as of December 31, 1979, by telephone contact, examination by the patient's personal physician, or examination at this medical facility. Functional classification according to New York Heart Association criteria was assigned each patient preoperatively and postoperatively.

Results

The operative mortality (before hospital discharge) in 25 patients undergoing aortic valve replacement, mitral valve replacement, or double-valve replacement was 6.25%, 14.03%, and 0, respectively (Table 2). No early death was due to valve malfunction. One death was due to sepsis and renal failure and the other, to myocardiopathic ventricular failure, which was the cause of the mitral regurgitation for which the patient underwent operation. There were no cerebrovascular accidents (thromboembolic events) in the early postoperative period.

Late postoperative survival in the three groups is illustrated in Table 3. The five-year survival for aortic valve replacement was 87.5%; for operative survivors it was 93.3%. The 1 late death occurred in a 74-year-old woman. It was due to perioperative myocardial infarction during removal of the dysfunctional aortic valve prosthesis five years following implantation. The valve failure manifested itself as substantial aortic stenosis with a 50 mm Hg peak systolic transvalvular gradient due to leaflet fibrosis.

Late postoperative survival after mitral valve replacement was 71.4% at 5 years (83.3% for operative survivors). The single death in this group occurred following repair of a perivalvular leak five years following original implantation. The explanted prosthesis showed no evidence of failure or fibrosis.

In the double-valve replacement group, 1 of 2 patients died in the 5 year follow-up period, for a survival of 50%. The death occurred out of hospital in a 70-year-old man. No definitive cause of death was determined, and no postmortem examination was done.

Valve Dysfunction

Valve malfunction occurred in 3 prostheses (3 out of 18) implanted in the aortic position. Two aortic prostheses developed substantial fibrosis and transvalvular gradients leading to clinical signs and symptoms of aortic stenosis, 1 in a 22-year-old woman and the other in a 74-year-old woman (as previously described). One of the aortic prostheses suffered the ravages of bacterial endocarditis, necessitating both mitral and aortic valve replacement four years following the original procedure. No mitral prosthesis became dysfunctional, although 1 prosthesis was removed because of a perivalvular leak (as previously described).

Therefore, a total of 4 valves (4 out of 27) required replacement: 2 for prosthesis dysfunction, 1 for prosthesis destruction secondary to endocarditis, and 1 for perivalvular leak. Two of the 4 patients survived reoperation and are doing well.

Thromboembolism

Among the 25 patients receiving 27 heterograft prostheses there were no documented thromboembolic events in the early or late postoperative periods. All patients were anticoagulated with warfarin sodium for eight weeks following operation. The warfarin was then tapered and discontinued irrespective of cardiac rhythm or findings at operation. The 1 patient with documented intraatrial thrombus at the time of double-valve replacement has remained in atrial fibrillation without anticoagulation or thromboembolism over the past five years.

Functional Status

Currently 80% of the patients (87% of surgical survivors) are alive, with the majority showing greatly improved exercise tolerance. According to New York Heart Association Functional Classification, all surviving patients are in Functional Class I or II. Approximately 86% (12 out of 14) of all aortic valve replacement patients are in Functional Class I, while only 40% (2 out of 5) of mitral valve replacement survivors are in this class. The patient who underwent both aortic and mitral valve replacement is in Class I. Valve dysfunction secondary to tissue changes in the bioprosthesis occurred in 7.4% (2 out of 27), requiring reoperation four to five years following original implantation.

Comment

The evolution of the bioprosthesis as a heart valve substitute has been prompted by the combined risks of thromboembolism and oral anticoagulation (hemorrhagic episodes) associated wih mechanical prostheses. The risk of thromboembolism in anticoagulated patients with mechanical prostheses has been reported by others [18] to be 6 to 10% per patient-year for hemorrhagic episodes. The mortality approached 1% per patient year for oral anticoagulation [18]. Certainly the risk of thromboembolism or hemorrhagic event is influenced by control of anticoagulaton therapy as well as by design and manufacturing materials of mechanical valvular prostheses. However, long-term anticoagulation is necessary with all mechanical prostheses.

The question of durability of bioprostheses remains unanswered. Tissue deterioration in the past has been well recognized with various methods of sterilization and preservation [5, 9, 10, 14, 15, 21]. The currently available glutaraldehyde-treated bioprostheses appear to have acceptable durability when mounted on flexible stents. The collagen cross-linking and intermolecular bonding achieved with glutaraldehyde treatment without sacrifice of pliability has produced encouraging clinical results. The present series, with 2 dysfunctional bioprostheses after four to five years of implantation in the aortic area, may temper this enthusiasm. A few bioprostheses are now approaching ten years of follow-up with as yet unavailable results. The functional durability of this small series of bioprostheses followed longer than five years compares quite favorably with the mechanical prostheses available over the same time.

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Tetralogy of Fallot Associated with Complete Atrioventricular Canal

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and Robert Lorenzo, M.D.

ABSTRACT **A 6-year-old girl had the clinical appearance of tetralogy of Fallot but was found at cardiac catheterization to have tetralogy of Fallot associated with complete atrioventricular canal. She underwent repair, and at recatheterization two years later, the hemodynamic result was excellent. Proper angiography is necessary to diagnose this combination, and correct preoperative diagnosis is necessary to plan a rational operative approach.**

Operative repair of tetralogy of Fallot and of complete atrioventricular canal is now routinely accomplished with a low mortality. The combination of these two complex lesions is unusual, and survival after corrective operation has been reported rarely [1, 2, 6]. Documentation of successful repair has been reported only once previously.

Failure of corrective operation is often due to inaccurate preoperative diagnosis [3], which leads to incomplete repair of the anomalies or prolonged operative time. Accurate preoperative diagnosis is essential to successful surgical repair. We therefore report the case of a patient with tetralogy of Fallot and complete atrioventricular canal to call attention to the unusual combination, review the diagnostic angiographic findings, and illustrate the procedure used for repair.

A girl with trisomy 21 syndrome was noted to be cyanotic while a neonate. She developed well, but at the age of 2 years started having hypoxic spells. The symptoms improved after a Waterston shunt, but reappeared two years later when she was 6 years old. Hypoxic spells were treated with propranolol, which had little effect. Chest roentgenogram at that time was consistent with tetralogy of Fallot, though the left pulmonary artery appeared dilated (Fig 1). Electrocardiogram showed right atrial and right ventricular hypertrophy with an indeterminate QRS axis.

Hemodynamic data at cardiac catheterization are shown in the Table. Right ventricular angiogram was consistent with tetralogy of Fallot. Left ventricular angiogram was consistent with complete atrioventricular canal (Figs 2–4). Aortic angiography demonstrated normal coronary artery anatomy, no evidence of aortopulmonary blood flow through the previously constructed Waterston shunt, and minimal deformity of the right pulmonary artery.

When she was 6 years 4 months old, the patient underwent corrective operation on cardiopulmonary bypass. As shown in Figure 5, the common atrioventricular valve had two common leaflets; the superior leaflet was unattached to the crest of the ventricular septum (Rastelli type C) [4]. The ventricular septal defect was very large, extending from the aortic valve under the crista supraventricularis to the inferior border of the atrioventricular valve annulus under the valve leaflets. The crista supraventricularis was rotated to the left and superiorly, in a manner typical of tetralogy of Fallot. The infundibular os was obstructed by hypertrophied muscle, and the pulmonary valve was bicuspid with severe commissural fusion.

Through a right atriotomy, the mitral and tricuspid components of both common leaflets were separated by dividing the leaflets parallel to the crest of the ventricular septum (Fig 6). Inferior chordal-septal crest attachments were divided. The lower half of a large oval knitted Dacron patch was sewn to the right side of the ventricular septum and to the aortic annulus, closing the portion of the defect below the atrioventricular valve annulus. The divided leaf-

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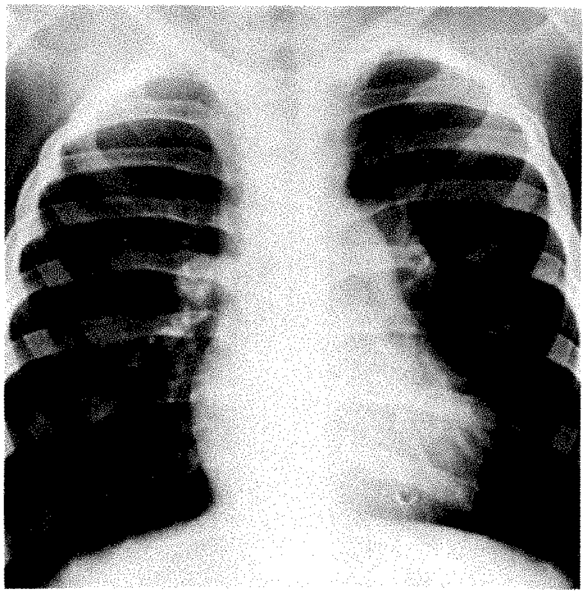

Fig 1. Posteroanterior chest roentgenogram shows a normal-sized heart with rounding of the left apex, dilatation of the proximal left pulmonary artery, and diminished pulmonary vascularity. The aortic arch is on the left.

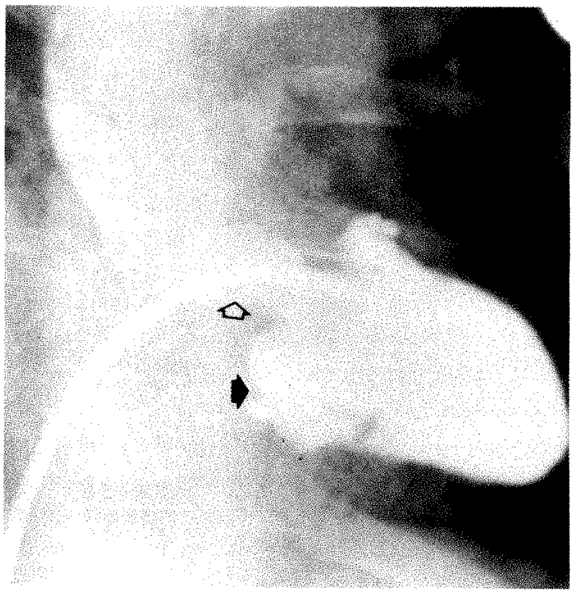

Fig 2. Anteroposterior projection of left ventricular angiogram shows the mitral valve to be deformed with scalloping of the right border of the left ventricle during early diastole (solid arrow). *An elongated channel connects the left ventricle with the aorta; its inferior border* (open arrow) *is formed by the displaced anterior leaflet of the mitral valve (gooseneck deformity). Severe atrioventricular valve regurgitation into both atria was apparent in subsequent frames.*

lets were attached to the prosthetic septum with pledgeted mattress sutures, with a single suture to buttress the corner of the mitral cleft and one for the tricuspid cleft. The upper half of the patch was sewn to the margin of the atrial septal defect. The fused pulmonary valve commissures were incised through a pulmonary arteriotomy.

The patient required small doses of dopamine by infusion to maintain an adequate blood pressure for two days following the procedure. Because of atelectasis and a large pulmonary right-to-left shunt, she required artificial ventilation for two days; the endotracheal tube was removed on the third postoperative day. Subglottic stenosis was treated with a series of bronchoscopies, dilatations, and injections of triamcinolone over three months; it has not recurred.

Four years after the operation, the patient has a murmur of mild mitral regurgitation and needs no medication. Heart size is normal, and she has no clinical evidence of congestive heart failure. Electrocardiogram shows right bundle-branch block with first-degree atrio-

Hemodynamic Data at Cardiac Catheterization

	Preoperative		Postoperative	
Site	Pressure (mm Hg)	O_2 Saturation (%)	Pressure (mm Hg)	O_2 Saturation (%)
Right atrium	11	70	8	77
Right ventricle	100/10	79	35/10	77
Pulmonary artery	. . .	. . .	25/10	76
Left atrium	12	92	. . .	. . .
Left ventricle	100/10	90	110/10	97
Aorta	100/60	88	110/75	96

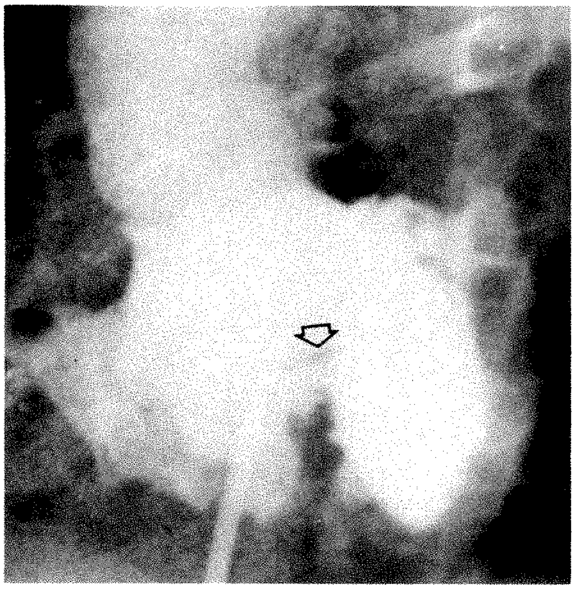

Fig 3. Left anterior oblique projection of left ventricular angiogram shows that the ventricular septal defect is limited by the aortic valve superiorly and extends into the region of the atrioventricular valves. Valve leaflet and chordae tendineae seem to stretch across the defect (arrow). *Note the extreme displacement of the aortic root over the right ventricle.*

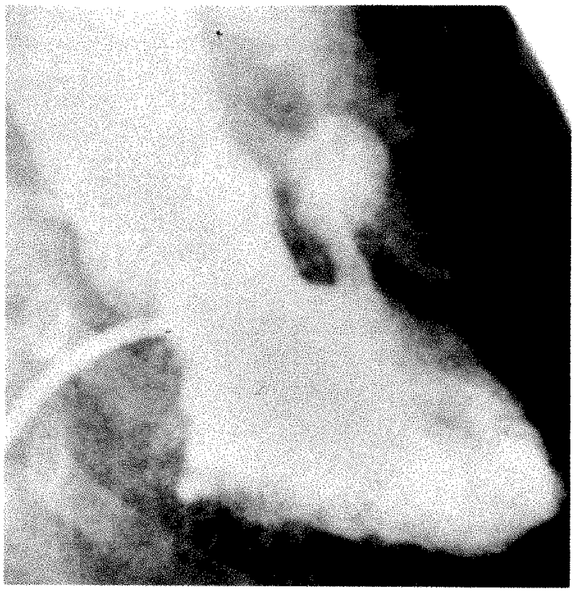

Fig 4. Right anterior oblique projection of left ventricular angiogram demonstrates stenosis of the infundibular os and doming of the stenotic pulmonary valve. The scalloped mitral valve is continuous with the aortic valve, demonstrated by the transmitral catheter abutting the aortic annulus.

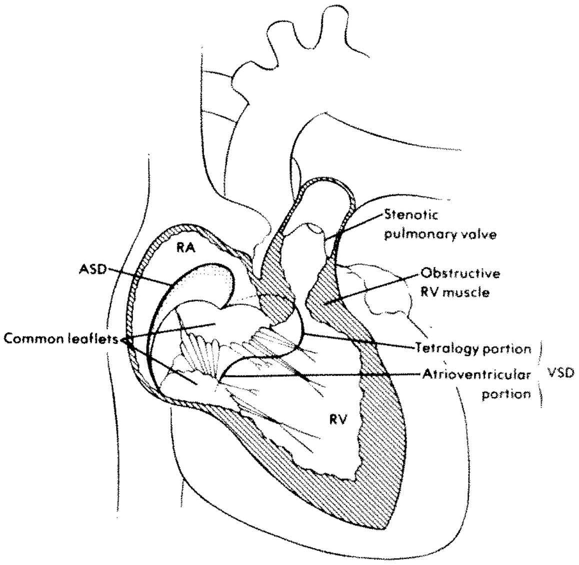

Fig 5. The low atrial septal defect was bordered by the atrioventricular valve inferiorly. (ASD = *atrial septal defect;* RA = *right atrium;* RV = *right ventricle;* VSD = *ventricular septal defect.)*

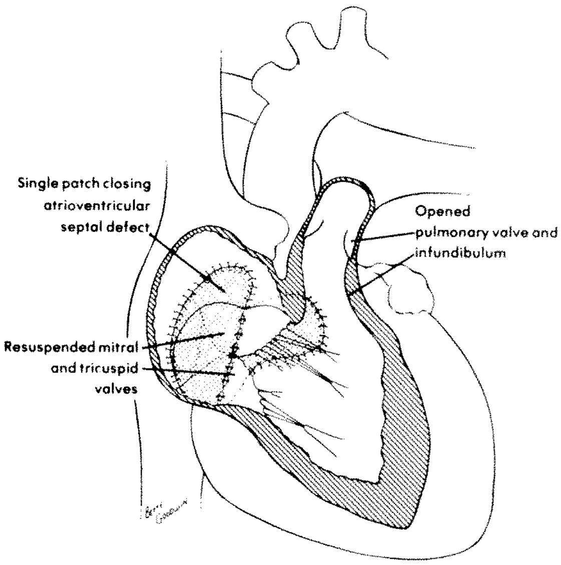
Single patch closing atrioventricular septal defect
Opened pulmonary valve and infundibulum
Resuspended mitral and tricuspid valves

Fig 6. Repaired malformation: obstructive septal and parietal band tissue was excised through a small right infundibulotomy.

ventricular block. Cardiac catheterization (see Table) and angiography were performed twenty-two months after operation.

Comment

Patients with the combination of tetralogy of Fallot and complete atrioventricular canal are seen with tetralogy of Fallot, cyanosis, cyanotic syncopal episodes (spells), and polycythemia.

Since palliative operation has met with little success [2], the primary approach should be repair. Only 3 patients in addition to the 1 reported here survived corrective operation [1, 2, 6].

The most frequent cause of death at the time of repair is failure to recognize the presence of complete atrioventricular canal preoperatively [6]. Trisomy 21 syndrome has been associated with the combined defect in more than 50% of the 39 previously reported cases [2, 6]. This is not surprising since tetralogy of Fallot and complete atrioventricular canal as isolated lesions are quite common in children with trisomy 21. The electrocardiogram usually demonstrates right ventricular or biventricular hypertrophy with pronounced left axis deviation and a counterclockwise loop in the frontal plane. These findings in a child with clinical evidence of tetralogy of Fallot should alert the clinician to the possibility of associated complete atrioventricular canal.

The definitive diagnostic study is cardiac angiography. We have emphasized the importance of left ventricular angiography in tetralogy of Fallot to detect associated anomalies of the left ventricular outflow tract [5]. This study is also necessary to uncover associated complete atrioventricular canal. The angiographic findings in the patient discussed are typical of patients with tetralogy of Fallot and complete atrioventricular canal.

Routine left ventricular angiography and alertness for the possible association of tetralogy of Fallot with complete atrioventricular canal should lead to consistent identification of the associated malformations prior to attempts at corrective operation. Once the lesion is recognized, a rational surgical approach can restore normal hemodynamics, as we have documented.

Addendum

While this manuscript was in press, 3 additional successful repairs of this malformation were reported (Pacifico AD, Kirklin JW, Bargeron LM Jr: Repair of complete atrioventricular canal associated with tetralogy of Fallot or double-outlet right ventricle: report of 10 patients. Ann Thorac Surg 29:351, 1980).

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Self-Conversion of Paroxysmal Atrial Tachycardia by Radio-frequency–Triggered Pacemaker

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ABSTRACT **The case of a 73-year-old woman with frequent disabling attacks of supraventricular tachycardia refractory to pharmacological therapy is presented. Successful management was achieved with a radio-frequency–activated pacemaker.**

Paroxysmal atrial tachycardia is well controlled with pharmacological agents in most instances and is usually quite benign. However, episodes of tachycardia can produce profound symptomatology if the ventricular rate is rapid or the episodes occur frequently. When the patient has major cardiovascular disease or is in the older age group, the tachycardia can be quite dangerous [7]. The recent advent of patient-activated rapid atrial stimulation using a radio-frequency transmitter has become a promising new modality for termination of refractory atrial tachycardia [2–6]. This report details the successful management of a patient with frequent paroxysmal atrial tachycardia by means of a radio-frequency pacemaker.

A 73-year-old woman had a history of paroxysmal atrial tachycardia from the age of 16 years. At the same age, a so-called toxic goiter was diagnosed; it first was treated with iodine and subsequently with subtotal thyroidectomy. She has remained euthyroid since, without need for thyroid replacement. However, she continued to average approximately forty-five episodes of atrial tachycardia per year. The tachycardia caused chest tightness, shortness of breath, and profound weakness. Occasional episodes lasted only minutes but the usual duration was hours and required treatment in the emergency room. The patient had been treated for years with digitalis, propranolol, quinidine, and combinations of these drugs without substantial benefit. Propranolol reduced the rate of atrial tachycardia from 160 to 120 beats per minute but the frequency of paroxysms remained the same. Tensilon (edrophonium chloride) administered intravenously in the emergency room often converted the atrial tachycardia to normal sinus rhythm.

On physical examination the heart rate was 60 beats per minute and regular. An atrial gallop was present at the apex. No murmurs or clicks were heard. She had bilateral femoral bruits. The remainder of the physical examination was unremarkable. Thyroid function studies were normal as were the other laboratory determinations. The electrocardiogram showed sinus rhythm with S-T segment and T wave changes secondary to administration of digitalis. The chest roentgenogram was within normal limits.

Electrophysiological Stress Testing

The patient was studied in the fasting condition without premedication. All medications were discontinued four days prior to the study. Two bipolar catheters, one for pacing and one for recording, were positioned in the high right atrium. One of these catheters was later positioned in the coronary sinus for left atrial recording and pacing. An esophageal bipolar catheter was placed at the level of the middle of the left atrium. His bundle electrograms were recorded from a catheter passed through the right femoral vein and positioned across the tricuspid valve. Three standard leads were also recorded simultaneously. Atrial pacing was performed at rates of 100 to 160 beats per minute for 30 seconds. Sinoatrial recovery time (SART), corrected SART (CSART), sinoatrial

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Electrophysiological Measurements

Variable	Initial Measurement (msec)	Second Measurement[a] (msec)
HR-LR	30	30
HR-LA	34	39
AH	70	65
HV	30	29
CSART	240	273
SACT	180	237

[a]Done ten minutes after 0.5 mg of ouabain administered intravenously.

HR = high right atrium; LR = low right atrium; LA = left atrium; AH = atrium to His bundle interval; HV = His bundle to ventricle interval; CSART = sinoatrial recovery time corrected for heart rate; SACT = sinoatrial conduction time.

conduction time (SACT), atrioventricular conduction times, and atrial conduction times were measured as previously described [1].

All electrophysiological measurements including intraatrial and interatrial conduction, atrium to His bundle (AH) and His bundle to ventricle intervals, CSART, and SACT were within normal range (Table). Atrioventricular Wenckebach phenomenon occurred with atrial pacing above 140 beats per minute.

An episode of atrial tachycardia spontaneously developed; this was initiated with a right atrial premature beat 340 msec following the preceding atrial electrogram (Fig 1). The tachycardia spontaneously converted to sinus rhythm. Atrial tachycardia also was initiated with the atrial extrastimulus method. An atrial premature depolarization 320 msec after the atrial depolarization (*a* wave) triggered atrial tachycardia at a rate of 143 beats per minute (see Fig 1). Tachycardia was terminated with atrial pacing at various rates (160 to 220 beats per minute) (Fig 2). The average atrial echo zone (interval from spontaneous atrial activity to atrial premature depolarization producing tachycardia) was 40 msec (320 to 360 msec). Evidence of dual atrioventricular node pathways was noted with a sudden prolongation of 140 msec in the H_1H_2 interval as the atrial premature depolarization was applied 20 msec earlier in the cycle (Fig 3). No evidence of accessory pathways was found.

Following the initial measurements, the procedures were repeated after a bolus of ouabain, 0.5 mg, administered intravenously. Tachycardia was again induced with atrial premature depolarizations and terminated each time with atrial pacing at a rate of 182 to 200 beats per minute. Ouabain narrowed the echo zone of tachycardia from 40 to 20 msec.

Because digitalis narrowed the echo zone, the patient was treated for a few weeks with high doses of digitalis. When this was found essentially ineffective, the decision was made to implant a permanent radio-frequency self-activated pacemaker.

Surgical Procedure

A right anterior thoracotomy was performed through the fourth intercostal space, extending medially to the internal mammary artery. The pericardium was opened 6 cm anterior and parallel to the phrenic nerve. The atrial appendage was relatively small. Two areas were selected on the atrial appendage 2.0 cm apart. A 4-0 Ethiflex suture was used to fasten the Medtronic 5813-A pediatric epicardial pacemaker lead onto the atrial appendage. The course of the stitch was as follows: through the hole in the atrial lead, through the lateral wall of the atrium, through the medial wall of the atrium, through a piece of thin Dacron felt, around back through the felt, through the medial aspect of the left atrium, through the lateral aspect of the atrium, and then through the adjacent second hole of the lead (Fig 4). A second stitch was placed in the bottom two holes of the lead in this same fashion.

A No. 11 blade was used to make an opening into the lateral wall of the atrium. The helix of the lead was placed into the atrium, and the sutures were tied. This made the helix bend against the inside of the atrium, putting as much surface area of the helix against the inside of the right atrial appendage as possible. Thus, electrode to atrium contact was obtained twice: first where it went through the lateral wall and second as the helix of the electrode was bent in the shape of a comma against the inside of the medial wall of the appendage. Another similar lead was sewn on the appendage 2.0 cm in-

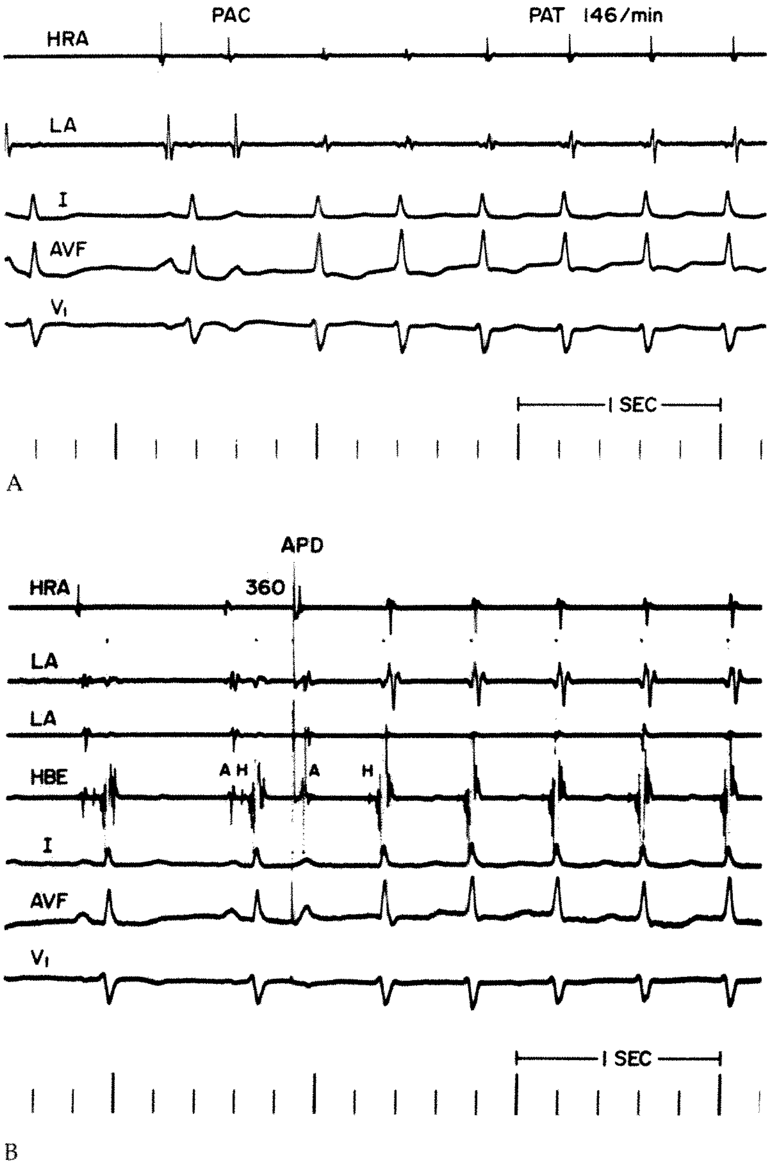

Fig 1. (A) Spontaneous paroxysmal atrial tachycardia (PAT) *(rate, 146 beats per minute) initiated with a right atrial premature beat 340 msec following the preceding atrial electrogram. (B) Tachycardia initiated with an atrial extrastimulus 320 msec following the preceding atrial electrogram. The atrium to His bundle interval is prolonged dramatically following the atrial extrastimulus. Note that the His bundle electrogram is always before the QRS interval and that the atria are activated after the His bundle.* (HRA = *high right atrial electrogram;* PAC = *premature atrial contraction;* LA = *left atrial electrogram;* APD = *atrial premature depolarization;* HBE = *His bundle electrogram;* AH = *atrium to His bundle interval.)*

feriorly. With the external 5300 Medtronic pacing unit, the threshold for atrial pacing was 2.7 ma with a pulse width of 2 msec.

A rather large loop of lead was placed inside the pericardium and a 2-0 gut suture used to fasten the two leads at their exit through the pericardium. The pericardium was then loosely closed with two additional sutures. Irrigation with bactericidal solution was carried out, and a chest tube was inserted for drainage. Closure of the ribs was routine, using gut around the ribs and interrupted gut sutures for subcutaneous tissues.

A subcutaneous pocket was then made for the receiver, Medtronic model 1515 RF atrial

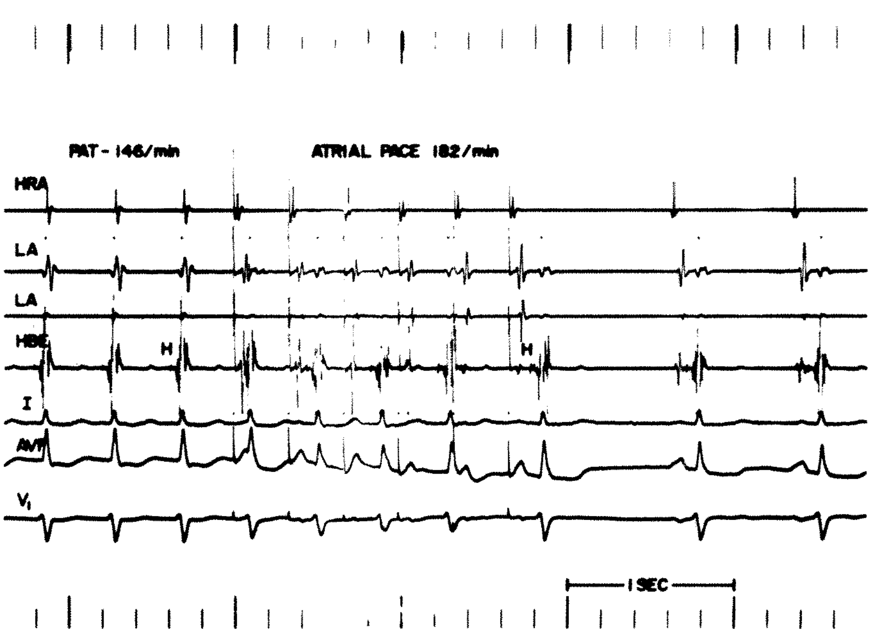

Fig 2. Termination of paroxysmal atrial tachycardia (PAT) *with atrial pacing at a rate of 182 beats per minute.* (H = *His bundle; other abbreviations same as in Figure 1.)*

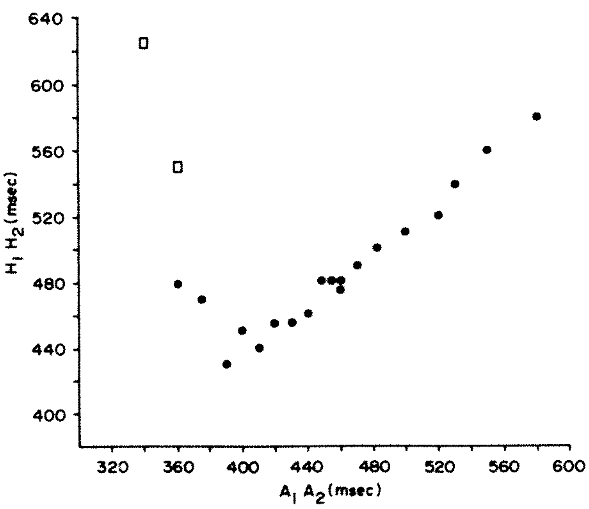

Fig 3. H_1H_2 *responses are plotted against* A_1A_2 *coupling intervals. The prolongation of the* H_1H_2 *interval occurs suddenly when the atrial premature depolarization is applied earlier in the cycle. When the fast atrioventricular node pathway becomes refractory, paroxysmal atrial tachycardia* (PAT) *results (open squares).* (A_1 *and* H_1 = *atrium and His bundle electrogram of the sinus beat;* A_2 *and* H_2 = *atrium and His bundle electrogram of atrial pace beat.*

pacemaker system, in the inferior half of the incision. The receiver was connected to the wires with the standard techniques. The correct side of the receiver was facing externally when placed in the pocket. At least 8 mm of tissue separated the receiver and the skin. The unit was tested again with the sterile transmitter supplied; again, atrial capture was obtained. The subcutaneous tissue and skin were closed appropriately.

Since the implantation of the pacemaker, every episode of paroxysmal tachycardia has been successfully converted to sinus rhythm with short bursts (1 to 3 seconds) of atrial pacing at rates of 160 to 180 beats per minute. The paroxysms have been terminated with two to six atrial paced beats applied one to five times. The patient is on a regimen of 0.25 mg of digoxin and 160 mg of propranolol daily. Eleven months after pacemaker implantation, she is in good health and pleased that she is able to convert each episode of tachycardia to sinus rhythm.

Comment

The patient presented a therapeutic dilemma because of the inability to control the tachycardia with drug therapy. She was selected for this therapeutic approach because of the frequency, duration, and symptomatology of the episodes, the inability of medication to sup-

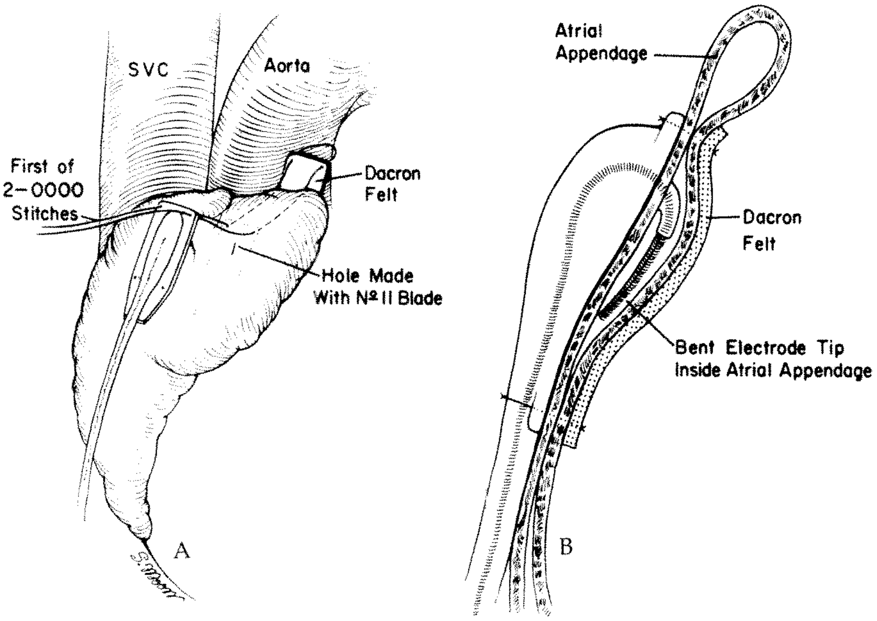

Fig 4. The first of two leads is sewn on the lateral aspect of the appendage. A second lead is placed 1 cm on either side. A No. 11 blade pierces only downward before insertion. (A) A sagittal view shows the bend in the helix inside the appendage and (B) a lateral view shows the increasing atrial wall contact. (SVC = *superior vena cava.)*

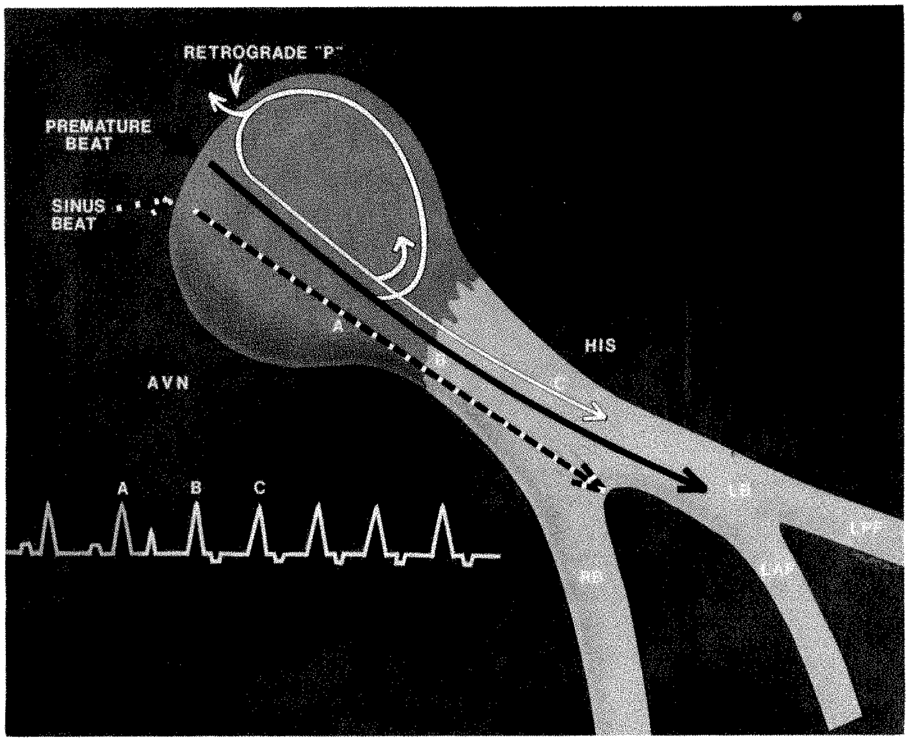

Fig 5. The mechanism of atrioventricular node (AVN) *reentry tachycardia. A sinus beat is conducted over the normal pathway* (A) *to the ventricle. An atrial premature beat* (B) *during its passage through the AVN enters the AVN abnormal pathway in a retrograde fashion and activates the atria again. The reentry loop is continued by conduction* (C) *again over the normal AVN pathway to the ventricle. Supraventricular tachycardia is thereby initiated.* (RB = *right branch;* LB = *left branch;* LAF = *left anterior fascicle;* LPF = *left posterior fascicle.)*

press the tachycardia, and the proved efficacy of terminating the tachycardia with overdrive pacing [6].

The patient's paroxysmal supraventricular tachycardia was demonstrated to be atrioventricular node reentry in type (Fig 5). This was indicated by the sudden increase in the AH interval following the premature atrial beat which triggered the tachycardia. The pattern of atrial excitation from low right to left, to high right atrium is typical for retrograde excitation from the atrioventricular node region. The "break" phenomenon of sudden change in the AH interval occurs when the "fast" atrioventricular node pathway becomes refractory and conduction through this node is by way of the "slow" pathway. The fast pathway then becomes the retrograde limb of the reentry loop, and tachycardia ensues. This type of supraventricular tachycardia usually is converted easily to sinus rhythm by atrial overdrive pacing.

Since the pacemaker is patient-activated and controlled, careful assessment of the patient's ability to use the device must be made. The patient should be emotionally stable, and presyncopal symptoms, syncope, or seizures should not occur at the onset of tachycardia. The patient must be able to recognize the rhythm disturbances and to initiate pacemaker stimulation. This mode of therapy has proved extremely effective in our patient. Radio-frequency pacemaker tachycardia control should be a relatively safe and reliable means of therapy in patients refractory to the usual medical management.

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Symptomatic Methemoglobinemia with a Commonly Used Topical Anesthetic, Cetacaine

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Richard C. Shaw, M.D., and John P. Connors, M.D.

ABSTRACT **Severe cyanosis resulting from acquired methemoglobinemia after application of a topical anesthetic, Cetacaine spray, occurred in a 37-year-old patient following bronchoscopy for postoperative atelectasis. Response to methylene blue therapy was dramatic and complete. Attention is drawn to a dangerous adverse effect of this commonly used topical anesthetic agent.**

Development of the fiberoptic bronchoscope has made therapeutic bronchoscopy an easier and more readily performed procedure in the management of postoperative atelectasis. Topical anesthesia provides a comfortable setting for the procedure and can be used in virtually all patients with few adverse effects when recommended dosage schedules are followed [14]. Cetacaine spray is a widely used and very effective agent for providing anesthesia of nasal, oral, and pharyngeal mucous membranes with elimination of the gag reflex. Adverse side-effects following its administration are rare. Asymptomatic methemoglobinemia has been reported [5], but to our knowledge, this is among the first reports of symptomatic methemoglobinemia after topical Cetacaine anesthesia.

A 37-year-old white woman with a history of rheumatic fever was hospitalized for evaluation. Severe mitral stenosis was diagnosed at cardiac catheterization, and mitral valve replacement was performed on March 19, 1979. The patient's immediate postoperative course was hemodynamically stable but total atelectasis of the right lower lobe was noted on the morning following valve replacement. Nasotracheal suctioning, intermittent positive-pressure breathing, and postural drainage failed to reexpand the involved lung. Therapeutic fiberoptic bronchoscopy was performed at the bedside under topical anesthesia with Cetacaine spray. The oral pharynx and nasal turbinates were sprayed using a Jetco cannula. Copious secretions were aspirated from the segmental bronchi of the right lower lobe followed by immediate reexpansion of the lobe.

Approximately thirty minutes following application of Cetacaine, circumoral and nail bed cyanosis was obvious despite the administration of oxygen, 5 liters per minute, by face tent. The inspired oxygen concentration was increased to 10 liters per minute, and blood gases showed a partial pressure of arterial oxygen of 94 mm Hg, a partial pressure of arterial carbon dioxide of 43 mm Hg, and a pH of 7.43 with a calculated oxygen saturation of 97%.* There was no change in systemic arterial pressure or right or left heart pressures.

The cyanosis persisted and was accompanied by somnolence and lethargy. A second blood sample was analyzed for methemoglobin, and the concentration was found to be 19% (normal is less than 1%).† Medications administered during the previous 6 hours included meperidine, penicillin, and oxacillin. Blood gases accompanying the episode are presented in the Table. Methemoglobin reductase levels were measured following the episode and found to be within the normal range. A total of 60 mg (1 mg per kilogram of body weight) of methylene blue was given intravenously as a 1% solution with complete resolution of the cyanosis within twenty minutes. A repeat

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*Corning 175 Automatic pH/Blood Gas System, Corning Medical Division, Corning Glass Works, Medfield, MA 02052.

†IL 282 CO-Oxymeter, Instrumentation Laboratory, Inc., Lexington, MA 02173.

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Blood Gas Values during Methemoglobinemia

Date	Time (hr)	F_{IO_2} (%)	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	pH	Calculated Oxygen Saturation (%)	MetHb (%)
3/20/79	1800	30	76	40	7.47	96	. . .
3/21/79	0415	30	121	43	7.43	98	. . .
	1200	30	115	40	7.47	96	0.8
	1900	30	94	43	7.43	97	Not obtained
	2000	40	84	44	7.44	97	19.0
Methylene blue given at 2030							
	2240	40	185	40	7.44	99	0.6
3/22/79	0630	30	98	40	7.44	98	. . .
3/23/79	0700	30	133	46	7.41	99	. . .

F_{IO_2} = inspired oxygen fraction; PaO_2 = partial pressure of arterial oxygen; $PaCO_2$ = partial pressure of arterial carbon dioxide; MetHb = methemoglobin.

methemoglobin level was less than 1%. The remainder of the hospital course was uneventful, and the patient was discharged on the twelfth postoperative day.

Comment

Methemoglobin is formed when reduced hemoglobin is oxidized and the heme iron is converted from the ferrous (HbFe++) to the ferric state (HbFe+++). This oxidized molecule is incapable of reversibly binding oxygen and carbon dioxide. Low levels of methemoglobin are produced continuously in the erythrocyte and exist in equilibrium with reduced hemoglobin (99 Hb:1 metHb). Methemoglobinemia occurs when the concentration of methemoglobin in circulating erythrocytes exceeds 1%. Erythrocytes contain a mechanism for maintaining hemoglobin in the reduced state utilizing the enzyme methemoglobin reductase. Methylene blue acts as a catalyst to enhance this reaction. Ascorbic acid is capable of nonenzymatically reducing methemoglobin. Many drugs and chemicals have been implicated in precipitating acute, toxic methemoglobinemia.

Acetanilid
Ammonium nitrate
Amyl nitrite
Aniline
Benzocaine
Bismuth subnitrate
Chlorates
Dapsone
Lidocaine
Naphthalene
Nitrobenzene
Nitroglycerin
p-Aminosalicylic acid
Phenacetin
Phenazopyridine
Prilocaine
Primaquine
Prontosil
Resorcinol
Silver nitrate
Sodium nitrite
Sulfamethizole
Sulfanilamide
Sulfapyridine
Sulfathiazole
Trichlorocarbanilide

Benzocaine-induced methemoglobinemia has been reported to occur following the cutaneous application of benzocaine as an ointment [8, 9, 19], a mucous membrane spray [18], and a suppository [2, 11, 12], after endotracheal tube lubrication [18], and after oral administration as a powder [1]. All these reports except that concerning oral administration involved children, and the methemoglobinemia was thought to develop as a result of a transient deficiency of erythrocyte methemoglobin reductase [16]. After oral administration of benzocaine, methemoglobinemia occurred in men, and the report had no mention of the status of reducing enzyme systems [1].

Cetacaine is the proprietary name for a product containing benzocaine (14.0%), butyl aminobenzoate (2.0%), tetracaine hydrochloride (2.0%), benzalkonium chloride (0.5%), and cetyldimethylethylammonium bromide (0.005%) [13]. In 1977, Douglas and Fairbanks [5] reported that 2 elderly patients, a man (77 years old) and a woman (80 years old), had methemoglobinemia following topical application of Cetacaine spray. Both patients rapidly became cyanotic but were improved following intravenous administration of methylene blue. No mention was made in their report of clinical symptoms. The blood of the male patient was assayed and found to contain a normal concentration of reductase linked to nicotinamide-adenine dinucleotide [10].

To our knowledge, this is among the first reports of symptomatic methemoglobinemia induced by Cetacaine and our patient is the third to experience this adverse reaction. Unlike the patients reported by Douglas and Fairbanks [5], the patient in this report was comparatively young and had much higher blood levels of methemoglobin (19% compared with 4.45% and 2.52%). However, our patient was similar to those previously reported in that cyanosis developed rapidly following exposure to Cetacaine. Intravenous administration of methylene blue dramatically abated the cyanosis, and no hemoglobin abnormalities could be detected. The somnolence, lethargy, and cyanosis cleared immediately following the institution of therapy in our patient. It is interesting to note that the calculated oxygen saturation was 97% when the methemoglobin concentration was 19% (see Table). This resulted from the use of two different instruments to perform a blood gas analysis. Reliance on the reported values could have led to an erroneous diagnosis. It is unfortunate that the CO-Oxymeter was used only for the methemoglobin determination. The marked improvement in partial pressure of oxygen after methylene blue therapy indicates the true progression of events more than does the modest change in calculated oxygen saturation. Further difficulties arise when the oxygen saturation is interpreted, even when it is measured directly, since methemoglobin concentration greater than 5% induces errors in the CO-Oxymeter method [6].

Smith and Olsen [17] published a comprehensive review of methemoglobinemia. The physiological features of methemoglobinemia are identical to hypoxia secondary to other causes. The most remarkable feature of hereditary methemoglobinemia is the appearance of surprisingly few adverse clinical effects despite circulating methemoglobin levels of up to 40%. However, acquired methemoglobinemia commonly produces severe clinical symptoms at much lower methemoglobin concentrations because compensatory mechanisms that develop in patients with the hereditary disorder do not exist in otherwise normal individuals. In addition, acquired methemoglobinemia increases the affinity of normal hemoglobin for oxygen, thus impairing the availability of oxygen at the tissue level as well as reducing the total oxygen supply [4].

In most patients, the clinical manifestations of acquired methemoglobinemia appear to correlate well with increasing methemoglobin concentration. Cyanosis is apparent at levels as low as 2.5% but clinical symptoms are rare below 20%. At concentrations between 20 and 50%, patients may complain of fatigue, weakness, dyspnea, headache, dizziness, or tachycardia. Methemoglobin concentrations in excess of 35% are usually associated with lethargy and stupor, and death occurs at concentrations greater than 70% [4]. In acquired methemoglobinemia, cyanosis clears in 24 to 72 hours after exposure to the causative agent is eliminated. Therapy is indicated when symptoms are disabling or stupor is persistent.

With the exception of a study demonstrating increased mortality in mice given 3-chloro-4-methylaniline to induce methemoglobinemia [7] and patients with glucose-6-phosphate dehydrogenase deficiency [15], intravenous administration of a 1% solution of methylene blue (1 to 2 mg per kilogram) is considered the treatment of choice for acquired methemoglobinemia [4, 17]. Clinical improvement of cyanosis usually occurs rapidly. If cyanosis persists 1 hour following the initial therapy, a second dose can be given. Methylene blue toxicity develops at levels higher than 7 mg per kilogram [4]. Ascorbic acid has not been shown to be of value in the treatment of acquired methemoglobinemia [3].

Review of the manufacturer's recommendations for the use of Cetacaine spray reveals that adverse, toxic effects can be seen when the agent is used on inflamed mucous membranes, though recommended dosage is not exceeded

[13]. It is postulated that inflamed mucosa increases systemic absorption of the topical spray. The patient described had no evidence of upper respiratory infection and no history of allergy. Recommended dosage schedules were followed.

Cetacaine contains 14.0% benzocaine. While larger doses of this drug are known to produce methemoglobinemia, the additive effects of other constituents such as tetracaine and the aromatic amino compound butyl aminobenzoate may combine to sufficiently oxidize the hemoglobin of susceptible individuals.

In summary, Cetacaine-induced methemoglobinemia is a rare and probably idiosyncratic reaction although a dose-related response cannot be excluded. Physicians, pharmacists, and other health care professionals should be aware of this potential complication, particularly in patients with compromised cardiorespiratory systems. The manufacturer of Cetacaine should be compelled to include this adverse effect in package information.

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NOTE

Atrial Pacing during Intraaortic Balloon Pumping

Douglas D. Payne, M.D., and Richard J. Cleveland, M.D.

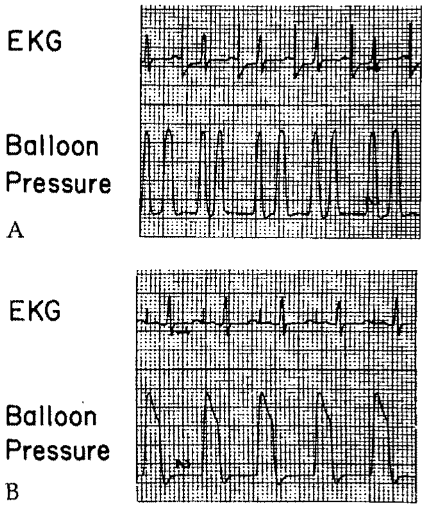
ABSTRACT **Intraaortic balloon pumping and atrial pacing are both useful in treating postoperative low output syndrome. However, the electrocardiographic atrial pacing spike can interfere with the electrocardiogram tracking mechanism of many balloon consoles. Bipolar epicardial pacing can avoid this problem and allow simultaneous atrial pacing and intraaortic balloon pumping.**

Atrial pacing is being used with increasing frequency after cardiac operations as treatment for nodal and sinus bradycardia, suppression of ectopic atrial or ventricular foci, and augmentation of cardiac output. Because of the common employment of intraaortic balloon counterpulsation for relief of myocardial ischemia and for treatment of cardiogenic shock, situations occur not infrequently in which both of these modalities are needed simultaneously.

However, not all balloon consoles are capable of ignoring or compensating for the atrial pacing spike. The AVCO model 7, for example, of which there are several hundred in use in the United States, senses the QRS complex on the basis of amplitude. When the atrial pacing spike is introduced into the electrocardiographic trace, it recognizes the atrial pacing spike as well as the QRS complex, and inflates twice during each cardiac cycle (Figure A). The problem can sometimes be solved by altering the position of the skin electrodes to find a lead with a QRS complex of greater amplitude than the atrial pacing spike. However, this cannot always be accomplished.

We have noted that the use of bipolar atrial pacing provides a much simpler alternative when atrial pacing and counterpulsation are considered necessary. Two atrial wires can be sutured close together on the right atrial wall, and these are connected to the positive and negative poles of the pacemaker. The minimum current necessary to provide consistent capture should be used. This method yields an atrial pacing spike that is of such a low amplitude in relation to the QRS complex that it will be ignored by the balloon console (Figure B). This has proved a useful method for us in "tricking" the AVCO model 7 during atrial pacing.

Some other consoles have been designed to deal with this problem, with varying degrees of success. We offer this method as a useful alternative for the problems of simultaneous atrial pacing and intraaortic balloon pumping, regardless of the type of balloon pump employed.



(A) Unipolar atrial pacing and (B) bipolar atrial pacing.

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COLLECTIVE REVIEW

Current Controversies in the Conduct of the Coronary Bypass Operation

Daniel J. Ullyot, M.D.

ABSTRACT **Recent reports comparing medical versus surgical management of patients with ischemic heart disease highlight the importance of technical quality in the interpretation of surgical results. This review is an attempt to examine current controversies in the conduct of coronary artery bypass with the purpose of suggesting strengths and weaknesses of alternative approaches. Topics include cold cardioplegia versus intermittent aortic occlusion, left ventricular venting, anastomotic technique, optical magnification, "complete revascularization," sequential versus individual grafting, internal mammary artery versus saphenous vein as conduits and the choice of alternative conduits when saphenous vein is unavailable.**

When coronary artery bypass is consistently performed with technical excellence, much of the controversy regarding medical versus surgical management is resolved in favor of surgical treatment [8]. The Veterans Administration Cooperative Study of chronic stable angina [14, 15] did much to emphasize the importance of technical quality in the analysis of surgical results [20].

The purpose of this review is to focus on selected controversial issues in the conduct of the coronary artery bypass operation with a view to suggesting strengths and weaknesses of alternative approaches and the circumstances under which one may be favored over another. There is no attempt to suggest a single best method but rather to provide a framework for choosing among a number of clinically useful approaches. In order to avoid ambiguity, I have indicated my clinical preferences at the end of each section.

The technical goals of coronary artery bypass are to construct bypass grafts to all major coronary arteries with proximal obstruction and satisfactory runoff and to accomplish this with minimal myocardial and noncardiac injury. There is general agreement about many aspects of the conduct of the procedure [13]. The current controversies can be classified for purposes of discussion into (1) myocardial protection, (2) anastomotic technique, and (3) selection of vessels and conduits.

Myocardial Protection

There is general agreement that coronary anastomosis is best performed during aortic occlusion to provide a dry, quiet field and to permit easy retraction of the heart. Two approaches have evolved to protect the myocardium during periods of interrupted coronary circulation: cold cardioplegia and interrupted aortic occlusion.

The former method depends on depressing myocardial metabolism by reducing myocardial temperature while all coronary anastomoses are constructed during a single period of aortic occlusion. The most common means of myocardial cooling is infusion of a cold, asanguineous solution into the aortic root [16]. Although some favor myocardial surface cooling as the exclusive means of myocardial cooling [1], this technique will be treated in the present discussion as adjunctive to myocardial cooling by aortic root infusion. Others advocate infusion of a cold, blood-containing solution for myocardial protection [5]. This variation on the technique of cold cardioplegia will not be considered here because it fails to provide the excellent coronary visualization achieved when the coronary circulation is washed out with a cell-free medium with apparently comparable protective effectiveness.

The alternative approach to myocardial protection is intermittent aortic occlusion. It depends on short periods of aortic cross-clamping during which a single coronary anastomosis is performed and is interspersed with periods of

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myocardial perfusion during which the aortic cross-clamp is removed while the aortic anastomosis is constructed.

The relative effectiveness of the two approaches to myocardial protection in terms of minimizing myocardial injury is beyond the scope of this discussion. Both approaches in experienced hands appear to be able to achieve comparable results in terms of operative mortality and rate of perioperative myocardial infarction [11, 18, 21]. These are, however, relatively insensitive indices of myocardial preservation. The next sections emphasize the technical implications of the two approaches as applied to the coronary artery bypass operation.

Cold Cardioplegia

The advantages of cold cardioplegia are as follows: (1) excellent visualization of the opened coronary artery; (2) easy cardiac retraction; (3) applicability in combined procedures when the aortic root is opened; (4) less manipulation of the atherosclerotic aorta (fewer cross-clampings are required and, if necessary, all aortic anastomoses can be done during the single period of aortic occlusion); and (5) a single "reperfusion" period. The physiological events occurring during the reperfusion period have yet to be fully elucidated. Theoretically, a single, longer reperfusion period following aortic occlusion might be better than several reperfusion periods associated with multiple aortic cross-clampings [2, 3].

There are several disadvantages of the cold cardioplegia technique. The first is uncertainty about homogeneous myocardial cooling. Some myocardial segments may not be cooled as well as others because of uneven distribution of the cold solution in the presence of coronary artery obstruction, and some might rewarm faster than others. These segments may be exposed to relatively long periods of ischemia when multiple grafts are done. The inability to discern when such damage might be occurring is the most important disadvantage of the method. The second disadvantage is hyperkalemia. With repeated infusions of hyperkalemic solution, the serum potassium may rise to levels inhibiting myocardial performance. I have observed at least 2 patients with a serum potassium in excess of 7 mEq per liter associated with bradycardia and hypocontractility who required the administration of glucose and insulin in order to be weaned from cardiopulmonary bypass.* The third is hemodilution. This method requires 800 to 1,500 ml of solution in addition to the usual priming volume. For this reason, we at the University of California Medical Center use blood in the prime more liberally so that the anticipated mixed venous hematocrit on bypass does not fall below 25%. The final disadvantage to cold cardioplegia is that it requires special solutions and apparatus.

We use cold cardioplegia in patients requiring multiple (three or more) grafts. We find exposure increasingly unsatisfactory with intermittent aortic occlusion when multiple grafts are constructed compared with that achieved with the cold cardioplegia technique. We also use it when a patient requires combined procedures or has severe atherosclerosis of the ascending aorta.

We avoid the technique in the presence of the following: (1) questions of aortic valve incompetence, and the ability to maintain a satisfactory pressure in the aortic root during infusion; (2) renal failure; (3) refrigerator failure; and (4) cold agglutinins. With reference to refrigerator failure, we have had isolated instances when the perfusate was improperly cooled. In such cases it was preferable to switch to a different method rather than wait for the perfusate to be cooled. As for cold agglutinins, an occasional patient will be found to have cold agglutinin activity at room temperature during routine blood typing. The possibility of red cell agglutination and consequent microinfarction at colder temperatures argues against the use of the cold cardioplegic technique in such a patient when alternative methods are available.

Our clinical application of the cold cardioplegia method of myocardial protection to patients undergoing coronary artery bypass is as follows: (1) Systemic hypothermia to 32°C is employed. (2) Left ventricular decompression

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*Since this manuscript was written, I now routinely use cold Ringer's lactate solution (K^+ 5 mEq per liter) for all subsequent infusions after the initial infusion and in patients with renal failure, for all infusions.

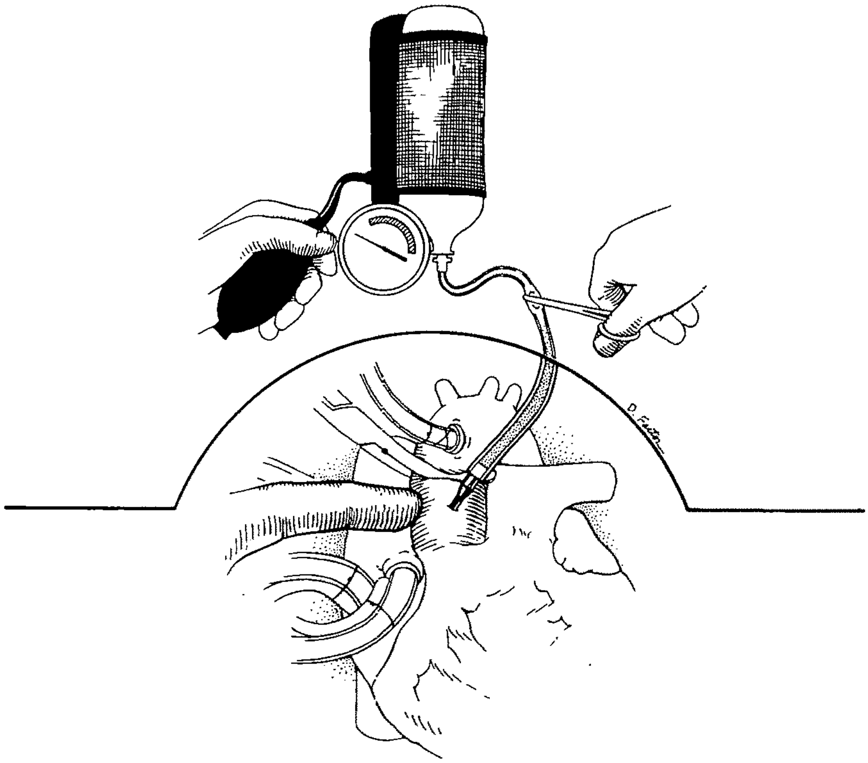

Fig 1. Cardioplegic solution delivery system.

reduces the rate of myocardial rewarming by draining blood returning to the left heart. (3) Individual caval cannulation reduces the rate of rewarming by more effectively (c.f., single atrial cannulation) preventing venous return from warming the right ventricle and right ventricular side of the septum. (4) Sites for coronary anastomosis are established prior to root infusion. The tissue overlying the site of proposed coronary anastomoses is incised prior to root infusion because surface anatomy is difficult to identify after blood is washed out of the coronary circulation. (5) Aortic root infusion is begun prior to aortic cross-clamping in order to maintain aortic valve competence. (6) Aortic root pressure is verified by palpation during infusion of solution. (7) Myocardial temperature is measured using a needle thermistor in order to verify effective cooling. We have observed as much as a 10°C temperature difference among various myocardial locations immediately after infusion. (8) Systemic perfusion pressure is reduced below a mean arterial pressure of 90 mm Hg (usual range, 50 to 60 mm Hg) during the period of aortic occlusion in order to decrease the rate of rewarming due to noncoronary collateral circulation. (9) Iced saline solution is applied topically at intervals during the ischemia period. (10) Cold cardioplegia solution is infused at 20- to 30-minute intervals if myocardial temperature rises above 18° to 22°C or if electromechanical activity is evident.* (11) Close attention is paid to preventing air embolism. The heart may suddenly and spontaneously defibrillate after the aortic cross-clamp is released (Figs 1, 2).

The cardioplegic solution used is a slightly alkaline (pH 7.6 to 8.1), slightly hyperosmolar (350 mOsm per liter), cold solution (4°C). It consists of the following: potassium, 20 mEq per liter; sodium, 27 mEq; magnesium, 3 mEq; chloride, 47 mEq; sulphate, 3 mEq; tromethamine, 2 mmole; and 5% dextrose. Approximately 800 ml is infused into the aortic root initially and 200 to 300 ml at 20- to 30-minute intervals during aortic occlusion. When the aortic root is opened for aortic valve replacement or replacement of the ascending aorta combined with coronary artery bypass,

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*Since this manuscript was written, I now routinely use cold Ringer's lactate solution (K^+ 5 mEq per liter) for these infusions.

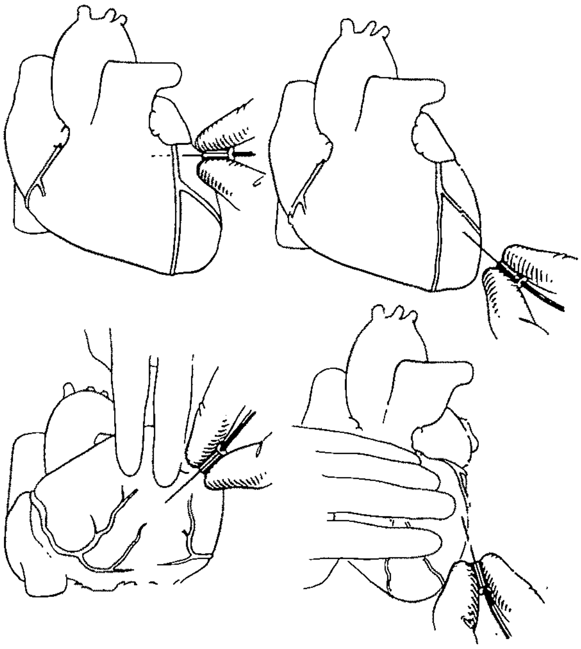

Fig 2. Myocardial temperature measurement.

the cold solution is infused directly into the coronary ostia using handheld cannulas. A simple delivery system is used consisting of a 1-liter plastic bag containing the cardioplegic solution and connected to plastic tubing (internal diameter, 3/16 inch or 0.5 cm), which is connected to a 13 gauge, short, beveled needle. The solution is delivered using a pressure bag regulated by the anesthesiologist. The needle is inserted into the aorta approximately 3 cm proximal to the aortic cannula. Later the needle hole is excised to become the site of one of the proximal anastomoses.

The safe duration of aortic occlusion using the cold cardioplegic technique is unknown. Our clinical experience suggests that one hour of aortic occlusion is well tolerated. Ordinarily this will allow four or five distal anastomoses to be accomplished with minimal myocardial injury.

Intermittent Aortic Occlusion

There are three major advantages of intermittent aortic occlusion. One is the opportunity to assess the heart at intervals between short periods of ischemia. Useful information about the heart's tolerance to successive periods of ischemia can be obtained by observing the beating heart during periods of coronary perfusion. Another is that it is easier to estimate the graft length in the perfused heart. Finally, no special solutions or apparatus is required.

The disadvantages are as follows: (1) relatively poorer exposure because of blood obscuring the opened coronary artery; (2) potential reperfusion injury since the myocardium is exposed to several reperfusion periods, thereby multiplying the putative damage ascribed to this interval; and (3) more manipulation of the aorta due to multiple cross-clampings. This may be important in the severely atherosclerotic ascending aorta.

Intermittent aortic occlusion is favored when few grafts are planned. The relative simplicity of the technique—usually done without left ventricular venting and without special solutions and apparatus—makes this approach attractive for patients requiring few grafts. When multiple grafts (three or more) are contemplated, the longer pump time, the increasing difficulty with exposure as the procedure progresses, and the theoretical concern about reperfusion injury outweigh the advantage of technical simplicity. The technique is to be preferred also when questions of aortic valve competence exist and when renal failure is present, magnifying concern about hyperkalemia.

Aortic valve incompetence of even minor clinical importance may pose a formidable problem if not recognized early in the conduct of coronary artery bypass. If aortic valve insufficiency is suspected, the left ventricle should be vented and the magnitude of the insufficiency evaluated in the arrested heart. If mean arterial pressure cannot be maintained in a satisfactory range (50 to 70 mm Hg) with good left ventricular decompression, the aortic valve should be replaced prior to the initiation of coronary artery bypass. If left ventricular decompression can be maintained with satisfactory mean arterial pressure, I favor intermittent aortic occlusion because of the uncertainties of myocardial cooling with root infusion under these circumstances.

Our technique of intermittent aortic occlusion is as follows: (1) Systemic hypothermia (32°C) is employed. This temperature usually will maintain ventricular fibrillation without spontaneous defibrillation during the period of aortic occlusion and will permit electrical defibrillation during intervals of coronary perfusion. (2) The decision to vent the left ventricle is left open with this technique (in the absence of aortic valve incompetence we commonly omit the vent in order to obviate an additional step in the procedure). (3) The heart is fibrillated electrically to obtain prompt cardioplegia, and (4) systemic perfusion is momentarily stopped and the aorta cross-clamped. This allows one to decompress the heart manually and to minimize mechanical injury to the aorta. (5) Single coronary anastomosis is performed, (6) the cross-clamp is removed, (7) the heart is defibrillated, and (8) the aortic anastomosis is performed. Cardiac action in the beating heart is assessed during this period with attention to the vigor of contraction and to the S-T segment displacement on the electrocardiogram.

Expeditious operation should be emphasized irrespective of the technique of myocardial protection since myocardial injury is a time-related phenomenon. I believe the number and physiological priority of bypass grafts should be established early in the procedure. If difficulties are encountered during the operation, it may be prudent to opt for fewer grafts. This cautionary approach is particularly relevant to patients undergoing combined procedures and to patients with very poor left ventricular function who are potential candidates for multiple grafts.

Left Ventricular Venting

The advantages of left ventricular decompression are several. It provides protection against left ventricular distention. This is particularly true in the presence of aortic valve insufficiency and also includes iatrogenic aortic insufficiency, sometimes encountered during cardiac retraction when the aorta is not cross-clamped and occasionally when a side-biting clamp is placed on the ascending aorta for proximal anastomosis with resultant distortion of the aortic valve. Also, it provides a dry field and reduces the rate of myocardial rewarming by more effectively draining blood returning to the left ventricle.

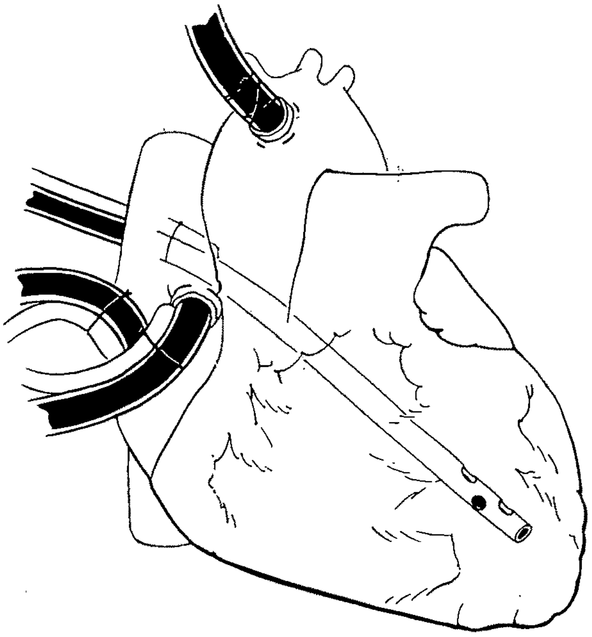

Fig 3. Left ventricular decompression.

The disadvantages are (1) risk of air embolism inherent with any incision in the left heart and particularly in the beating heart during cardiopulmonary bypass, (2) an additional step tending to prolong the procedure, and (3) a potential source of bleeding, left atrial laceration, or dislodgment of endocardial thrombus.

Left ventricular decompression is employed under the following circumstances: (1) aortic valve insufficiency; (2) poor left ventricular function—preoperative ejection fraction less than or equal to 0.3—or increased end-diastolic pressure or volume (the damaged left ventricle is more vulnerable to distention); and (3) use of cold cardioplegia. Removal of blood entering the left ventricle reduces the rate of myocardial rewarming. Figure 3 shows placement of the vent through the right superior pulmonary vein.

Individual Caval versus Single Atrial Cannulation

There is disagreement about whether individual vena cava cannulation is preferable to single atrial cannulation for venous drainage. The advantage of individual caval cannulation is *consistently* better venous drainage especially during cardiac retraction when obstruction at the caval-atrial junctions is apt to occur. It is my experience that single atrial cannulation using a No. 40 cannula inserted through the right atrial appendage, with multiple side holes, and with the tip placed in the inferior vena cava provides satisfactory venous drainage in many cases. However, individual caval cannulation provides greater consistency in this respect and is favored for procedures requiring cardiac retraction, such as placement of posterior grafts or combined mitral valve replacement and coronary artery bypass, and the cold cardioplegic technique. When cold cardioplegia is employed, the rate of myocardial rewarming due to entry of blood into the right ventricle, can be reduced.

Aortic versus Femoral Artery Cannulation

The discussion of aortic versus femoral artery cannulation is concerned with technical considerations unrelated to myocardial protection but is included in this section for convenience. In general, aortic cannulation is preferred to obviate groin dissection. Femoral artery cannulation is favored when a redo procedure is being performed, when there is a short ascending aorta in a patient requiring multiple grafts or combined procedures, and when there is severe atherosclerosis of the ascending aorta.

Femoral artery cannulation is avoided in the presence of abdominal aortic aneurysm because of the potential hazard of cerebral embolization of atherosclerotic debris with retrograde perfusion, and severe peripheral vascular disease.

Anastomotic Technique

The anastomotic techniques commonly employed are interrupted, continuous with fixation at ends, and continuous without fixation. I favor continuous technique without fixation because it is faster and more hemostatic in my experience than when the interrupted technique is used and provides better visualization for placement of stitches at the ends of the anastomosis (Fig 4) and a better size match by allowing the arteriotomy to be extended compared with continuous technique with fixation at both ends (Fig 5). The disadvantage of continuous technique without fixation is the potential problem of "pursestringing" the anastomosis when the single, double-armed suture is tied.

The technique of coronary anastomosis employed at the University of California Medical Center is depicted in Figures 6 through 10. A single, double-armed monofilament polypropylene suture is used. In order to prevent "pursestringing," the vein graft is irrigated with saline solution while the suture is tied with just enough force to stop major leaks (Fig 10). This irrigation maneuver has the additional virtues of augmenting myocardial cooling when the cold cardioplegic technique is used (the graft is irrigated with solution at 4°C when the cold cardioplegic technique is employed), providing an estimate of runoff, and flushing through micro air bubbles that may be trapped in the coronary microcirculation. With this suture technique, graft patency was 89% (266 out

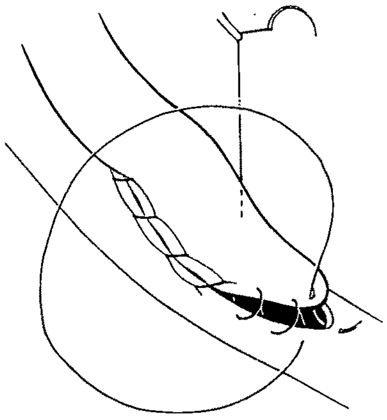

Fig 4. Placement of outflow sutures.

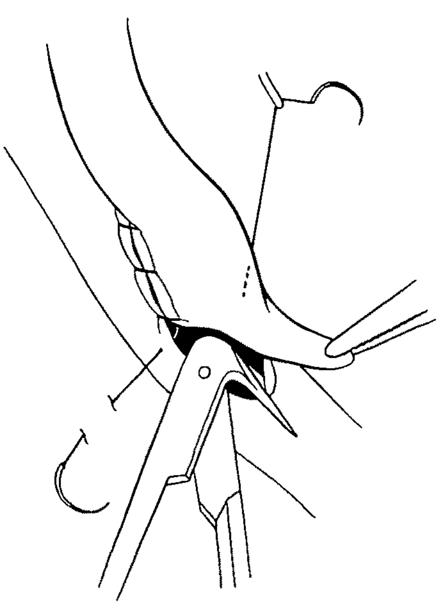

Fig 5. Incision in the apex of the coronary artery.

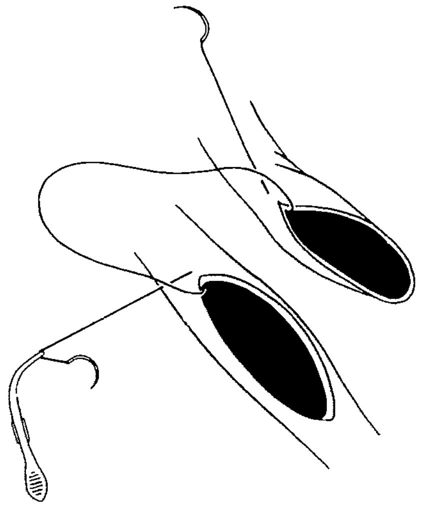

Fig 6. Coronary artery anastomosis: first stitch.

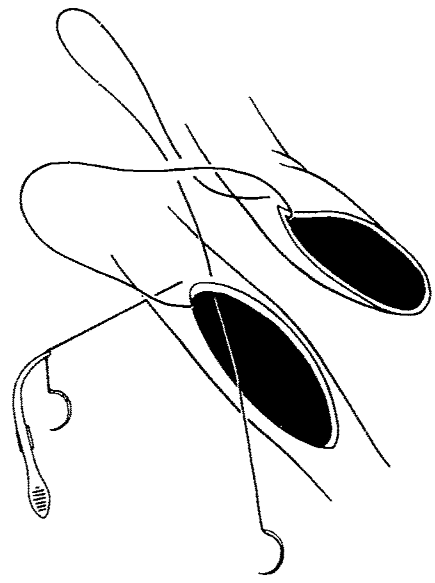

Fig 7. Coronary artery anastomosis: outside to inside on artery; inside to outside on vein.

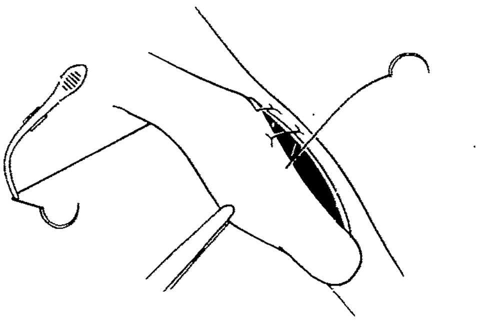

Fig 8. Coronary artery anastomosis: first quadrant completed.

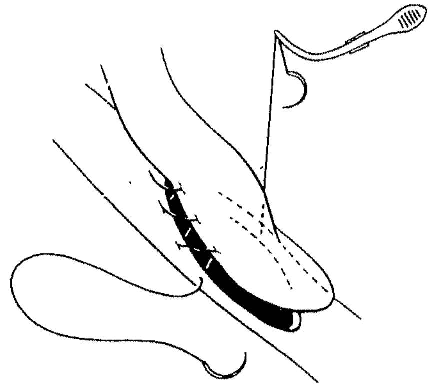

Fig 9. Coronary artery anastomosis.

of 299) at a mean follow-up of 8.1 months in a study of 118 randomly selected patients.

We employ continuous 5-0 Prolene for aortic anastomosis also without fixation (Figs 11, 12). A 4 mm button of aorta is excised using a punch.

Interrupted technique using 7-0 silk is used for internal mammary artery anastomosis. Manipulation of the fragile internal mammary artery is minimized with a "no touch" technique.

Optical Magnification

The controversy about optical magnification is seldom heard nowadays. I believe that the single most important adjunct to precise, expeditious, small-vessel anastomosis is the use of binocular loupes and fiberoptic illumination. I use four and one-half power optical magnification and a fiberoptic headlight in all cases [19].

Selection of Vessels and Conduits

Complete Revascularization

The concept of complete revascularization is widely embraced as an important goal in the surgical management of coronary artery disease. Yet considerable disagreement exists regarding the interpretation of this principle [4, 10]. For example, in patients with high-grade proximal stenosis of the right coronary, left anterior descending coronary (LAD), and left circumflex systems and satisfactory runoff, some surgeons consider complete revascularization to mean one graft to each system. Others faced with a similar patient place multiple grafts to individually obstructed branches within each

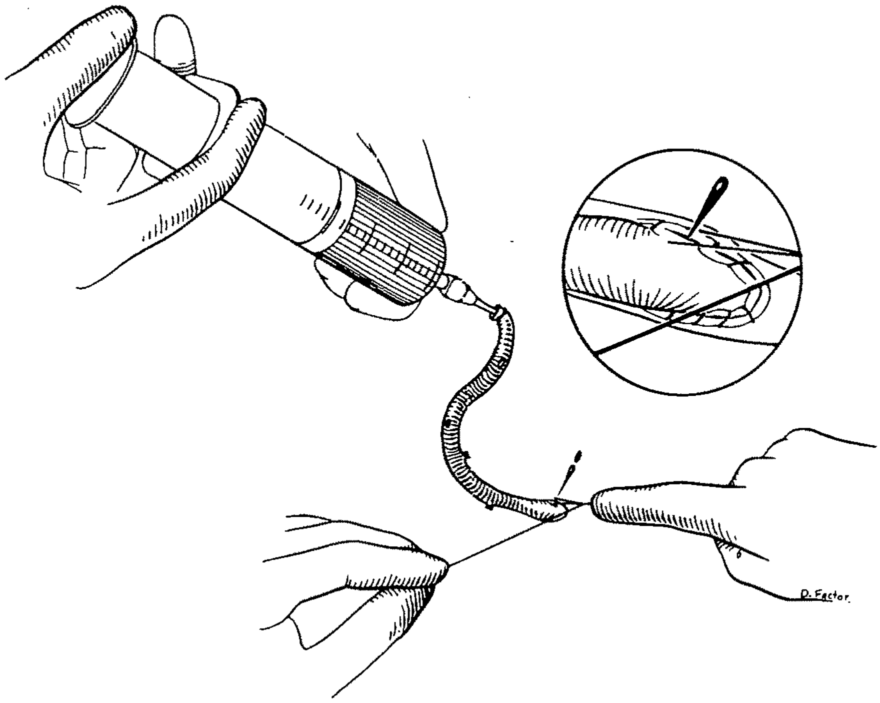

Fig 10. Coronary artery anastomosis: irrigation maneuver.

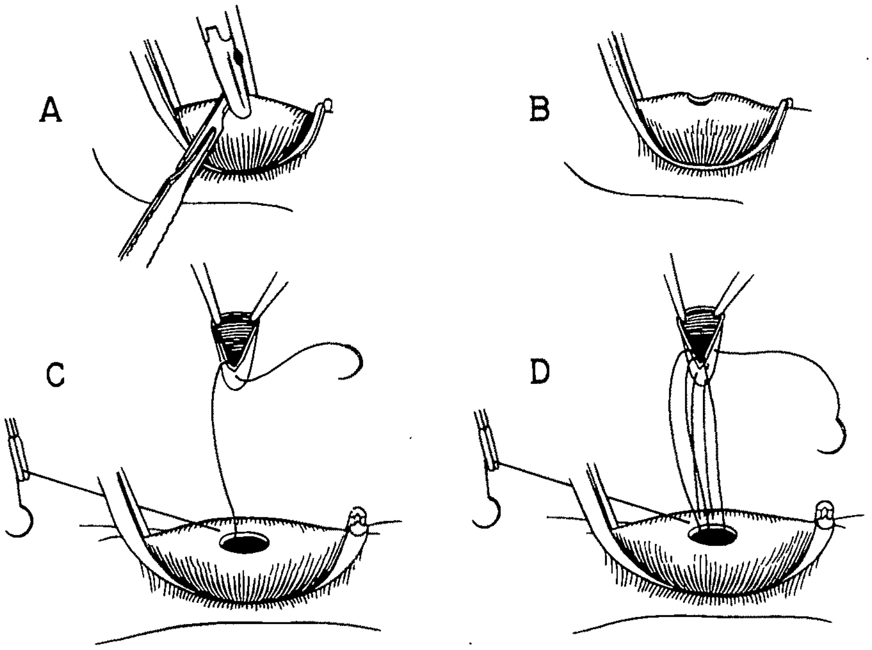

Fig 11. Steps in the construction of the aortic anastomosis.

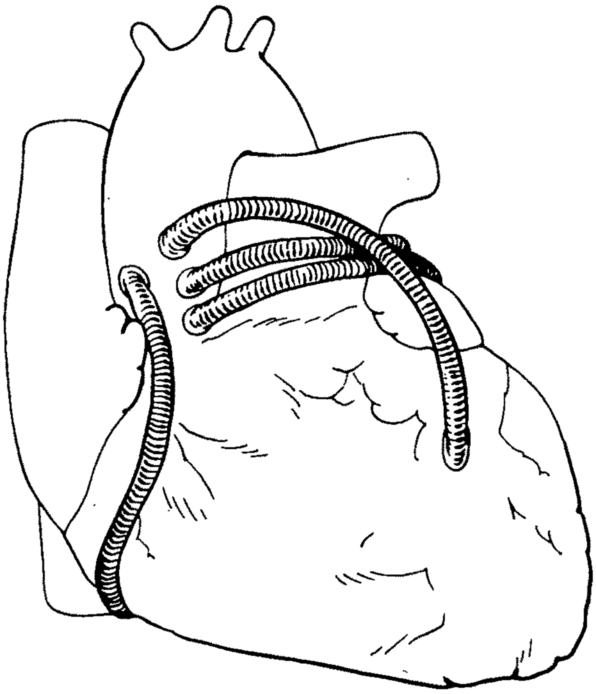

Fig 12. Orientation of vein grafts.

system including small vessels (luminal diameter of less than 1.5 mm) and vessels with mild (less than 50%) proximal stenosis.

As a first approximation, all major coronary vessels with 50% or more proximal stenosis, a luminal diameter greater than or equal to 1.5 mm, and with satisfactory runoff to segments of viable myocardium are potential candidates for bypass. These include the LAD, major diagonal branches of the LAD, rarely large septal perforating branches of the LAD, the right coronary artery, the posterior descending coronary artery, and left ventricular branches of the left circumflex and right coronary systems. I have not favored bypass to the left circumflex trunk in the atrioventricular groove or to acute marginal or right ventricular branches of the right coronary artery.

I believe that it is possible to assign priorities to each coronary bypass based primarily on angiographic data. Additional information regarding the suitability of vessels for bypass can be obtained by incising the tissues over the sites for prospective coronary artery anastomosis and careful inspection of the vessel using optical magnification. Time spent in careful identification of vessels for anastomosis as well as the optimal segment for graft placement deserves emphasis. For example, the identification of a large intramyocardial branch of the left circumflex system for bypass is of greater benefit than multiple bypasses to small, superficial branches.

The data necessary to refine the concept of complete revascularization are unavailable. The contribution of each graft to a defined clinical result is difficult to assess when multiple grafts are placed. The economist's concept of "diminishing marginal utility" [17] can be applied to the question of how many grafts to place by asking: "What benefit in terms of augmented myocardial blood flow is gained by the placement of each additional bypass graft, taking into account luminal size, runoff, competitive flow, and the cost in terms of myocardial and noncardiac injury associated with longer ischemia and pump times?" It is clear that in order to answer this question, many factors, such as myocardial reserve, angiographic interpretation, technique of myocardial protection, and surgical skill and experience, must be considered. Postoperative studies of graft patency and ventricular function are invaluable in evolving one's own interpretation of complete revascularization. Simply stated, the decision about how many grafts to place must be carefully individualized, taking into account each patient's findings and the surgeon's own experience.

I commonly place three or four and occasionally five grafts in patients with extensive coronary artery disease and suitable vessels for bypass. I sound a cautionary note in placing more than three to five grafts, particularly in patients with poor left ventricular function or those undergoing combined procedures. The utility of additional grafts must be weighed against the consequences of longer ischemia and pump times, particularly in patients with diminished myocardial reserve.

Coronary Endarterectomy

Mechanical endarterectomy combined with bypass grafting to the endarterectomized segment is employed when an endarterectomy plane inadvertently develops in the course of entering a vessel through an atherosclerotic segment. It is preferable to complete the endarterectomy in such instances particularly when the lumen is smaller than anticipated. Rarely, it is desirable to perform a deliberate endarterectomy combined with bypass grafting to an obstructed right coronary artery when the distal vessels are patent and too small to accept a graft.

Sequential versus Individual Grafting

There is disagreement about whether sequential or individual grafts are preferable. The advantages of sequential grafting are a reduction in the number of aortic anastomoses, conservation of conduit material, and the potential for improved graft patency. It is suggested that stasis and consequent thrombotic occlusion is less likely in a conduit with multiple runoff, particularly when grafting to small coronary arteries in which individual graft flow might be expected to be low.

The disadvantages of sequential grafting are its technical difficulty and the potential for multiple graft failure due to proximal occlusion. Technical factors such as the length of interanastomotic graft segments and the potential for graft distortion at the sites of side-to-side anastomoses are more demanding with this technique. Studies have shown satisfactory early patency in experienced hands [7]. Graft patency superior to that achieved with individual vein grafting over a long follow-up has not been established.

I employ sequential grafting when more than four vessels are bypassed (the number of aortic anastomoses is limited arbitrarily to four) and when severe atherosclerosis of the ascending aorta is present. I regard sequential grafting as a technical adjunct rather than as a means of achieving improved patency. Figures 13, 14, and 15 show examples of sequential grafts used.

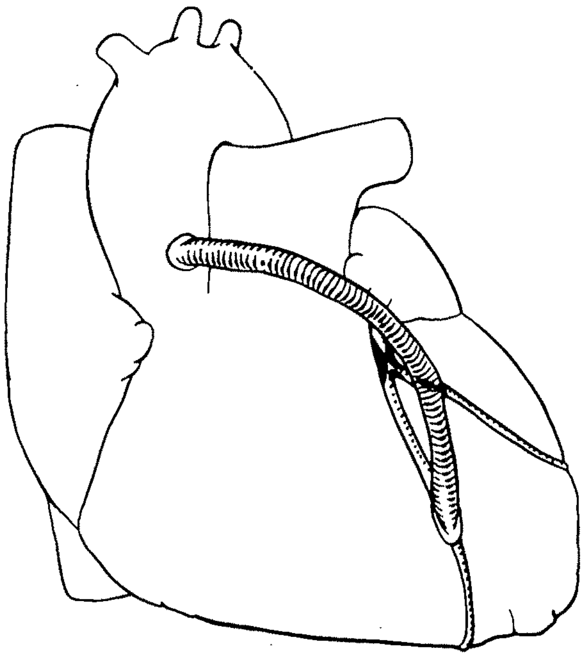

Fig 13. Sequential grafting: left anterior descending coronary artery–diagonal branch.

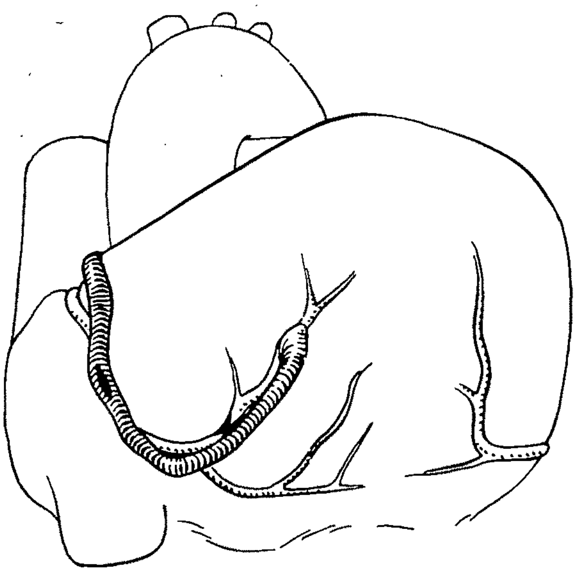

Fig 14. Sequential grafting: posterior descending coronary artery–right coronary artery.

Internal Mammary Artery versus Saphenous Vein

Considerable controversy remains about the use of the internal mammary artery as a bypass conduit. The advantages of the internal mammary artery are better early graft patency [6], potentially better graft longevity with artery-to-artery anastomosis [12], and obviation of the need for an aortic anastomosis. The disadvantages associated with the use of this artery are (1) its greater technical difficulty, (2) flow limitation, (3) limited applicability (only two bypasses using both internal mammary arteries are possible and ordinarily they are not useful for posterior coronary grafts), and (4) creation of more postoperative chest wall discomfort [9].

I use the internal mammary artery in the following situations: (1) when saphenous vein is

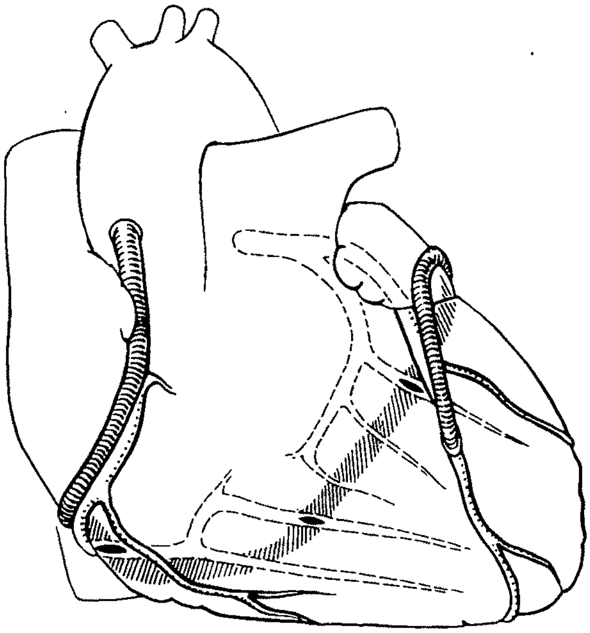

Fig 15. Sequential grafting: single aortic anastomosis.

not available; (2) in young patients in whom long-term graft durability is a more compelling consideration; (3) when the ascending aorta is severely atherosclerotic and aortic anastomosis is technically inadvisable; (4) in patients with severe hyperlipidemia (the vein graft is probably more vulnerable to subsequent atherosclerosis than the artery graft in such patients) [9]; and (5) in patients with previously failed vein grafts not obviously due to technical factors.

The internal mammary artery is avoided under the following conditions: (1) in emergency procedures; (2) when unusually large graft flow is anticipated (left ventricular hypertrophy, left main occlusion); (3) when proximal stenosis is moderate (50 to 75%) since the internal mammary artery appears to function poorly in the presence of competitive flow; and (4) when bypassing posterior vessels.

Our technique is as follows: (1) mobilization of the internal mammary artery pedicle using electrocautery; (2) performance of coronary artery vein graft anastomoses prior to internal mammary artery anastomosis to avoid trauma to the implanted internal mammary artery during cardiac retraction; and (3) testing flow in the internal mammary artery prior to implantation. The internal mammary artery is rejected if flow is low or if the vessel is clearly smaller than the proposed coronary artery for bypass. (4) We use an interrupted anastomotic technique using 7-0 silk employing a "no touch" technique to the fragile internal mammary artery and (5) fix the pedicle of the internal mammary artery to the epicardium.

Alternative Conduits

When greater saphenous vein and internal mammary artery are unavailable, I use the following conduit material in descending order of preference: lesser saphenous vein, cephalic vein, saphenous vein allograft, and Gore-Tex. Autogenous material is strongly favored over either homograft or synthetic conduit material.

Conclusion

This review based on my clinical experience is offered to stimulate further discussion about the optimal conduct of the coronary bypass operation. It is acknowledged that the several steps in the procedure, discussed separately for purposes of clarity, are intimately interrelated. The validation of various approaches to an isolated step in the procedure is complicated because clinical end points reflect the totality of surgical management, including patient selection, anesthetic management, surgical skill and experience, and postoperative care. Indeed, the resolution of these controversies toward a single, best method may not only be impossible by objective means but may be undesirable. The wide variety of clinical exigencies presented to the surgeon demand versatility. When several alternative operative approaches are understood and mastered, the surgeon is able to respond more specifically and more effectively.

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Heparin Anticoagulation

To the Editor:

An article on heparin anticoagulation during bypass by Roth, Cukingnan, and Scott was published recently (Ann Thorac Surg 28:69, 1979). The authors recommended the use of the activated coagulation time (ACT) for monitoring the level of anticoagulation. While I have no quarrel with the recommendation, the reason given, i.e., to prevent "the adverse effects of overheparinization and excess protamine," misses the major point at issue. The major risk is not too much heparin but too little, with the precipitation of disseminated intravascular coagulation (DIC).

An adequate dose of heparin for the average patient is easy to determine. However, in a patient population of reasonable size (N = ~ 100), patients vary fourfold in their heparin sensitivity and threefold in the rate at which heparin is degraded [1]. Heparin requirements thus span a twelvefold range. Whatever the amount of heparin required by the average patient, there will be some who require six times more and others who need six times less. Too much heparin, particularly if it is adequately neutralized at the end of bypass, is probably relatively harmless. It is the group that receives too little heparin that is in danger. Admittedly, the number of patients at risk is small, probably not more than 1 to 2%, but for them the lethality of DIC is extremely high!

The heparin metabolism of real patients undergoing bypass can be studied in a computer model and the amount of heparin needed by a particular patient can be determined. Such computer simulation studies using a protocol identical to that employed by Roth and co-workers suggests that fewer than 5% of an average group of patients would be at any serious risk, with perhaps 1 to 2% so markedly underheparinized that DIC would be likely. Their failure to identify a case of DIC in their group of 28 patients is not surprising.

Historical and some anecdotal evidence supports these conclusions. The diagnosis of classic DIC was made fifteen times during a three-year period, 1970 to 1973, prior to the institution of the ACT monitoring procedure at my institution. Some 900 extracorporeal procedures were performed during this time; the approximate incidence of postoperative DIC was 1.7%. Since use of the ACT has become routine, there have been no instances of DIC in more than 3,000 bypass procedures. In fact, a study designed to explore the pathophysiology of DIC in patients after bypass was abandoned because there were too few cases.

The "more or less" note by the Editor at the end of the article by Roth and associates is both more or less correct and more or less misleading. On reading that the ACT is "more or less, an overall assay of all coagulation factors, including platelets," some readers might assume that a normal postoperative ACT effectively rules out the possibility of continued bleeding due to defects in platelet number or function or both of these conditions. In fact, the opposite is true. While the ACT does require a few platelets to act as a phospholipid catalyst in the terminal phases of the coagulation pathway, the number required is well below that needed for normal hemostasis. Nor do platelets that function in the ACT necessarily function well in vivo. If inadequate surgical hemostasis is excluded from consideration, continued postoperative hemorrhage in the face of a normal ACT virtually always means a platelet problem.

Finally, both the article and the note infer that excess protamine is a major cause of postoperative bleeding. The animal experiments on protamine overdosage employed doses of 10 mg per kilogram of body weight or more. It is to be hoped that a corresponding excess in humans is seldom seen clinically. A single additional dose of 0.75 mg per kilogram administered after the calculated neutralizing dose has failed to normalize the ACT has been proved both safe and diagnostically precise at Loma Linda University Medical Center. If such an additional dose of protamine fails to normalize the ACT or at least shorten the clotting time substantially, then other causes for continued bleeding must be sought. Unneutralized heparin is not the culprit.

Brian S. Bull, M.D.

Loma Linda, CA

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Rehn's Cardiorrhaphy

To the Editor:

"Surgical Management of Traumatic Intracardiac Injuries" by Whisennand and colleagues (Ann Thorac Surg 28:530, 1979) was both an interesting article and another "benchmark" of accomplishment from the Cora and Webb Mading Department of Surgery. However, it is perhaps all the more revealing to note that Rehn's successful cardiorrhaphy for trauma was performed not in 1847 but in 1897 [1, 2]. Even in Houston, fifty years may encompass more than a lifetime!

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SEVENTEENTH ANNUAL MEETING OF THE SOCIETY OF THORACIC SURGEONS

Los Angeles, CA
January 26–28, 1981

The Seventeenth Annual Meeting of The Society of Thoracic Surgeons will be held at the Los Angeles Bonaventure Hotel, January 26–28, 1981.

Application for Membership
(Deadline: September 1, 1980)

Requests for application forms for membership in The Society of Thoracic Surgeons should be addressed to Quentin R. Stiles, M.D., Chairman, Membership Committee, The Society of Thoracic Surgeons, 111 E Wacker Dr, Chicago, IL 60601.

The completed application forms and supporting letters must be in the hands of the Membership Committee by **September 1, 1980,** for the applicant to be considered for election at the meeting next January.

Call for Abstracts—1981 Meeting
(Deadline: August 31, 1980)

Abstracts for papers to be presented at the 1981 annual meeting are now being accepted. The deadline for receipt of abstracts is **August 31, 1980.** An original and 9 copies should be submitted, using the official Society abstract form (on verso of this page), to W. Spencer Payne, M.D., Chairman, Program Committee (Abstracts), The Society of Thoracic Surgeons, 111 E Wacker Dr, Chicago, IL 60601. Additional forms are available upon request from the Society. Abstracts must summarize an original contribution not presented or submitted elsewhere. Abstracts received after the deadline will not be considered. It is requested that the covering letter indicate the author who is to receive notice of acceptance or rejection and the author who will present the paper.

Essayists are reminded that according to the bylaws of the Society, all papers accepted for presentation: (1) must be submitted in duplicate to the Secretary at the time of presentation or to the Editor of *The Annals of Thoracic Surgery* prior to presentation; and (2) become the property of the Society if they are accepted for publication, in which case they may not be published other than in *The Annals of Thoracic Surgery.*

It is well recognized that abstracts frequently belie their content by virtue of poor organization, and as a result valuable contributions to the Scientific Sessions may be unrecognized. It is important that methods and results be clearly defined in the abstract; therefore, general statements such as "results will be presented" are not acceptable. When a procedure or method is stated to have "advantages," those advantages should be defined. Abstracts that simply summarize results without defining objectives and methods are equally undesirable.

Speakers for accepted papers are limited to 10 minutes.

Instructions for Abstracts

The official abstract form printed on verso of this page and available from the Society, or photocopies thereof, must be used. Authors must categorize the principal subject of their abstract using the code at the top of the form, and insert the proper code in the box provided in the upper left corner of the form.

1. Full names of authors must appear on the abstract.
2. Institution or address is to be given, but omit titles, degrees, and appointments.
3. Abstracts must be limited to 250 words and must be typed double-spaced.
4. When percentages are used, the absolute numbers of derivation must be stated.
5. The body of the abstract should include:
    a. A brief statement of the purpose of the study being presented, with reference to the current state of research in the field.
    b. The methods of study or experimental approach, clearly but briefly defined.
    c. A summary of the results and/or conclusions of the study, including sufficient details to support those conclusions.
    d. A statement concerning the significance of the work and its possible implications for future research; "results will be presented" is unacceptable.
6. The form must be signed by the senior author attesting that the material will not be published elsewhere if accepted for publication in *The Annals of Thoracic Surgery.*

In discussion of papers, the Society encourages a healthy spirit of constructive critical review and rebuttal by comments pertinent to the content of the paper being presented. Presentation of discussion in the form of "secondary papers" will not be welcomed.

Call for Surgical Films
(Deadline: August 31, 1980)

The popular surgical movie program will again be presented at the Los Angeles meeting. The Program Committee hereby solicits the submission of surgical films, which may portray a surgical procedure or simply a technical maneuver that the surgeon thinks will be of interest to the Society. The film may not exceed 10 minutes in length. Sound movies are acceptable but not necessary, and live narration by the principal surgeon is a requirement for participation in the movie night program. The movies may be on Super-8 or 16-mm film. The deadline for submission of films is **August 31, 1980.** Films also should be sent to W. Spencer Payne, M.D., Chairman, Program Committee, at the Society office, 111 E Wacker Dr, Chicago, IL 60601.

W. Gerald Rainer, M.D.
Secretary

AUTHOR INSERT CODE

THE SOCIETY OF THORACIC SURGEONS

Abstract Form

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T = Trauma
TX = Transplantation
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GV = Great vessels
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HC = Congenital

HCA = Coronary
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END = Endoscopy

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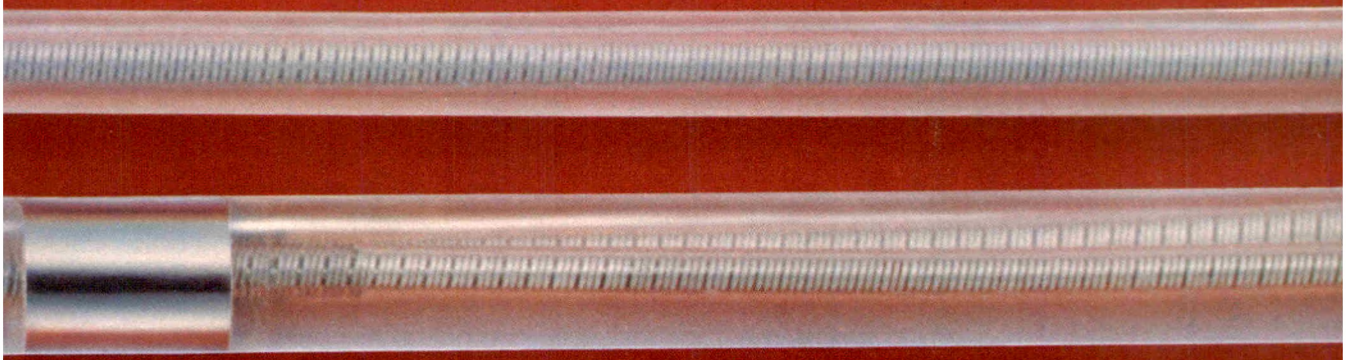

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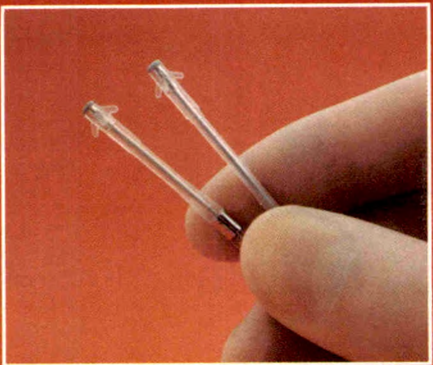

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Please submit full information with each ad, including name, address, and telephone number of contact person. If anonymity is desired when advertising a position wanted or available, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in *The Annals* Editorial Office and will be conveyed to the advertiser shortly after receipt.

Ads must be submitted no later than eight weeks prior to the publication month of the desired issue. Send ad and *nonrefundable* check (in the amount of $25 for every 50 words times the number of issues the ad is to run), payable to *The Annals of Thoracic Surgery*, to: Herbert Sloan, M.D., Editor, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

SITUATIONS WANTED

Experienced **cardiac and thoracic surgeon,** 41, seeking to relocate. Six years' experience in an active private practice; trained at major midwestern university. ABS, ABTS certified. Will consider all areas. Curriculum vitae upon request.

Please respond to W-221, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Thoracic and cardiovascular surgeon, 37, ABTS, ABS certified. Well trained in all facets of thoracic, cardiac, and peripheral vascular surgery, including angio-access. Seeking affiliation leading to partnership with cardiothoracic group. Available immediately.

Please respond to W-225, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiothoracic surgeon, 39, ABS, ABTS certified, presently in private practice for two years, desires to relocate. Experienced in all facets of adult cardiac surgery.

Please respond to W-226, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Thoracic, cardiovascular surgeon, certified, 48, university trained. Cardiovascular residency, 1971. Very experienced thoracic, vascular, angiograms, dialysis access, pacemakers. Moderate open-heart experience. Could develop rapidly in active practice because of previous experience. Understands physiology. Will consider any location, solo, group, with or without open heart.

Please respond to W-229, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon, 35, well trained at major university center, seeks faculty position or association with private group. No geographic preference. Available immediately.

Please respond to W-231, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon, 35, ABS, ABTS Part I, one year of experience in a very busy cardiovascular and thoracic surgery program. Would like to relocate and prefers Southeast, but will consider other locations.

Please respond to W-232, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon wishes to relocate. ABS, ABTS certified, university trained; publications, three years' experience in adult cardiac, thoracic and vascular surgery in private practice. No geographic preference.

Please respond to W-233, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiac anesthesiologist, 32, Board certified, trained in all aspects of open-heart surgery, seeks to join or establish cardiac anesthesia practice. Available immediately.

Please respond to W-234, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon, ABS, ABTS certified, in private practice, wishes to relocate. Trained at major institution. No geographic preference. Curriculum vitae upon request.

Please respond to W-235, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Thoracic and cardiovascular surgeon, 38, ABS, ABTS certified, full-time professor at university, seeks opportunity to relocate practice. Available immediately.

Please respond to W-236, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

SITUATIONS AVAILABLE

Cardiothoracic and vascular surgeon wanted to join two-man group in eastern Pennsylvania. Must be ABTS certified or eligible. Would prefer someone genuinely interested in living in this area.

Please response to A-186, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Full-time position available in growing southeastern **university cardiac surgery program.** Clinical ability, teaching and research interests required.

Please respond to A-189, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Thoracic and cardiovascular surgeon wanted. Ninety-member multispecialty group adjacent to modern, accredited 480-bed hospital with a cardiovascular intensive care unit seeks Board-eligible or Board-certified specialist to join three thoracic and cardiovascular associates. Located in university metropolitan area of 105,000 in upper Midwest, 35 minutes from superb lake region. Associated with four-year medical school. Salary negotiable. All specialities represented. Will pay expenses for physician and spouse for interview.

Please respond to A-194, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular thoracic surgery fellowships (2) start July 1, 1980. Active open-heart program; clinical cardiovascular research opportunity; at least three years of surgical training required. Stipend plus attractive fringe benefits. Rental housing available; annual conference attendance provided.

Contact Dr. Adrian Kantrowitz, Chief, Cardiovascular Surgery, Sinai Hospital of Detroit, 6767 W Outer Dr, Detroit, MI 48235; tel: (313) 493-5775.

Fellowship in cardiovascular surgery available. Applicants should have completed general surgical training. Excellent opportunity for clinical and research experience in cardiovascular surgery offered. University cardiovascular program.

Please respond to A-199, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

The Chicago Heart and Lung Hospital is under construction at 6500 S Pulaski Rd for the management of cardiovascular and lung diseases exclusively, including open-heart surgery. **Applications are being accepted for Board-certified cardiologists, thoracic and cardiovascular surgeons, and cardiac anesthesiologists.** Apply immediately while there are still openings on the staff.

Send letter of interest and curriculum vitae to Grant Gilbert, Heart, Lung and Vascular Institute of Chicago, 7000 W North Ave, Chicago, IL 60635.

Thoracic and vascular surgeon, Board certified or eligible, **wanted** by group in southeast Florida. No open-heart; practice limited to thoracic and major arterial surgery with active vascular laboratory facility.

Please respond to A-201, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiac surgeon wanted to develop new open-heart surgery program. Presently performing 30 catheterizations per month and referring over 125 patients per year for surgery. Association will be with large multispecialty group.

Please submit curriculum vitae to Mr. Wyman Taylor, Administrator, Great Falls Clinic, 1220 Central Ave, Great Falls, MT 59401.

General/vascular surgeon, Board eligible or Board certified in thoracic surgery. Multispecialty group, 29 physicians, with 4-physician general surgical department actively recruiting an additional physician. Currently 1 Board-certified thoracic surgeon, 3 Board-certified general and cardiovascular surgeons in department. Graduates with university-affiliated postgraduate training preferable.

Please respond to Administrator, Palm Beach Medical Group, 705 N Olive Ave, West Palm Beach, FL 33401.

One-year fellowship in adult cardiac surgery in a university-affiliated teaching hospital **available 1980.** Prior thoracic experience desirable.

Please reply to Cardiovascular Surgery Associates, Suite 501, St. Thomas Medical Building, 4230 Harding Rd, Nashville, TN 37205.

Associate sought in private practice limited to cardiac, thoracic, and peripheral vascular surgery. Rural area in Midwest. Practice expanding rapidly. ABTS required.

Please respond to David S. Starr, M.D., 1393 Mt. Everett, Hubbard, OH 44425; tel: (216) 568-7433.

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YOUNG INVESTIGATORS' AWARD FOR 1981

1st prize:	$1000.00
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The North American Society of Pacing and Electrophysiology (NASPE) invites submission of manuscripts for competitive review and eventual presentation of the 1st and 2nd prize-winning papers at its 2nd Annual Scientific Symposium on March 14, 1981, in San Francisco, CA. The goal of this award is to encourage and give recognition to able young investigators for original investigation or basic research in the area of cardiac pacing and/or cardiac electrophysiology.

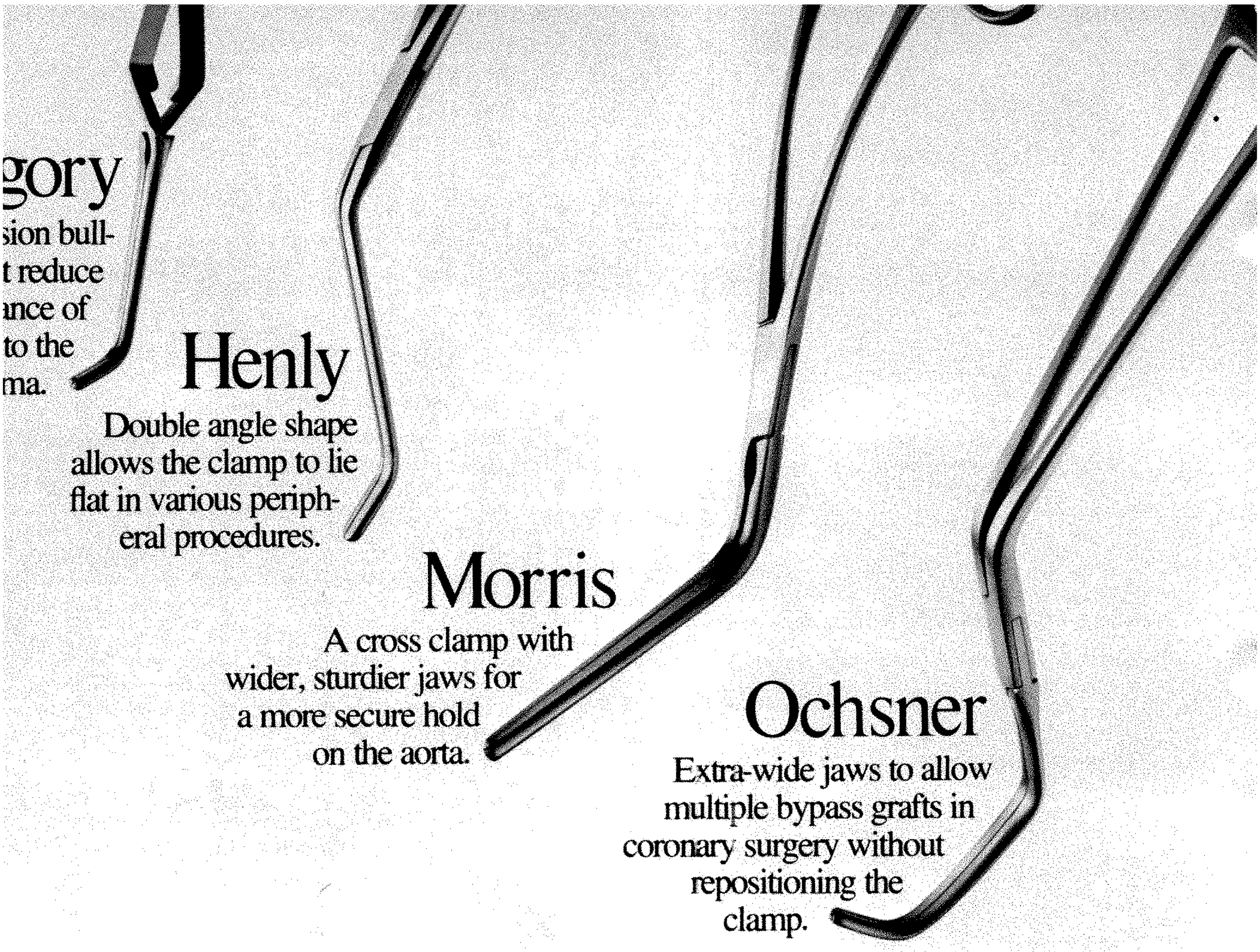
Eligibility
Any physician or scientist who is presently involved in an active fellowship or residency program or who has been involved within the past three years is eligible to participate. This includes medical students and PhD candidates. Applicants must reside within or have received their academic training within the geographic boundaries of North America (i.e., Canada, United States, Greenland, Mexico, Central America, Caribbean Islands).

**Deadline for Submission of Manuscripts:
December 15, 1980**

Rules
1. The investigation upon which the manuscript is based must be an original piece of investigation performed predominantly by the first author.
2. The applicant must attest that the investigation has not previously been reported or published elsewhere and that, if chosen by the judges as a prize-winning entry, it will not be presented or published prior to March 14, 1981.
3. Award-winning manuscripts will be published in PACE: The Journal of Pacing and Electrophysiology.
4. Abstracts of non-award winning manuscripts deemed by the judges to be of high reader interest will be published in PACE.
5. Authors of award-winning manuscripts are expected to attend the 2nd Annual Scientific Program of NASPE both for presentation of a 15-minute summary of their manuscript (1st and 2nd prize only) and receipt of awards.

For application forms and further information, contact: Dr. Seymour Furman, Program Chairman 2nd Annual Scientific Program, NASPE, c/o Montefiore Hospital, 111 East 210th Street, Bronx, NY 10467.

Support for this Award has been provided by a Professional Education Grant by Medtronic, Inc.



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The indications for permanent pacing in the presence of acute myocardial infarction have not yet been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, mechanism of the arrhythmias, and response to therapy. In general, symptomatic drug-resistant bradyarrhythmias which impair cardiac output are considered indications for pacing in patients with acute myocardial infarction, regardless of infarct location.

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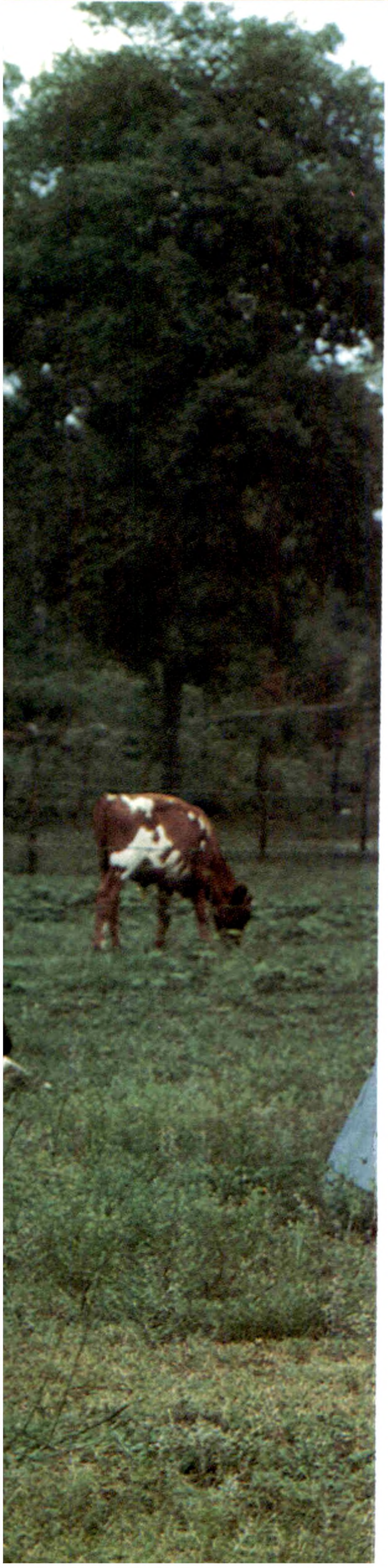

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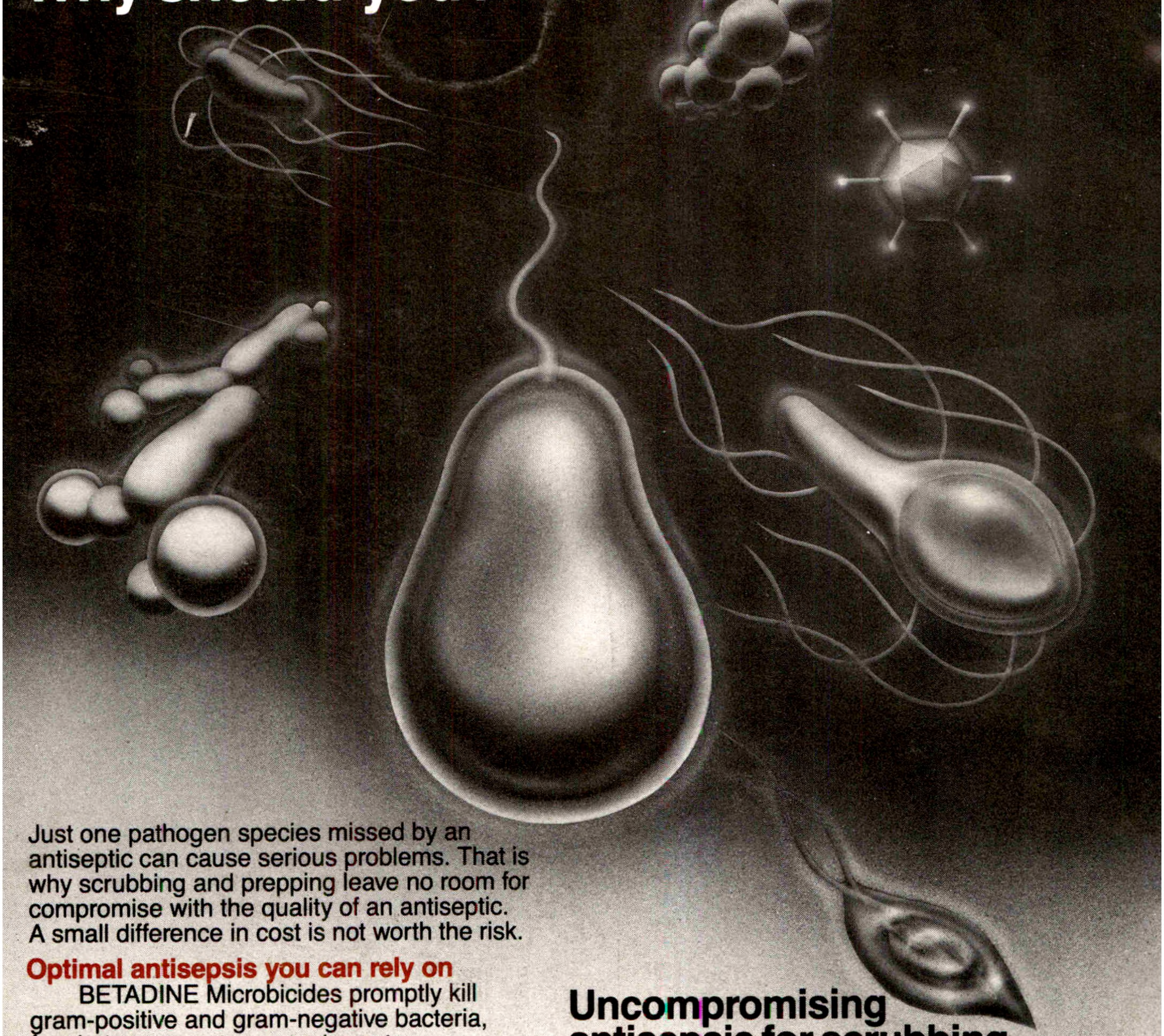

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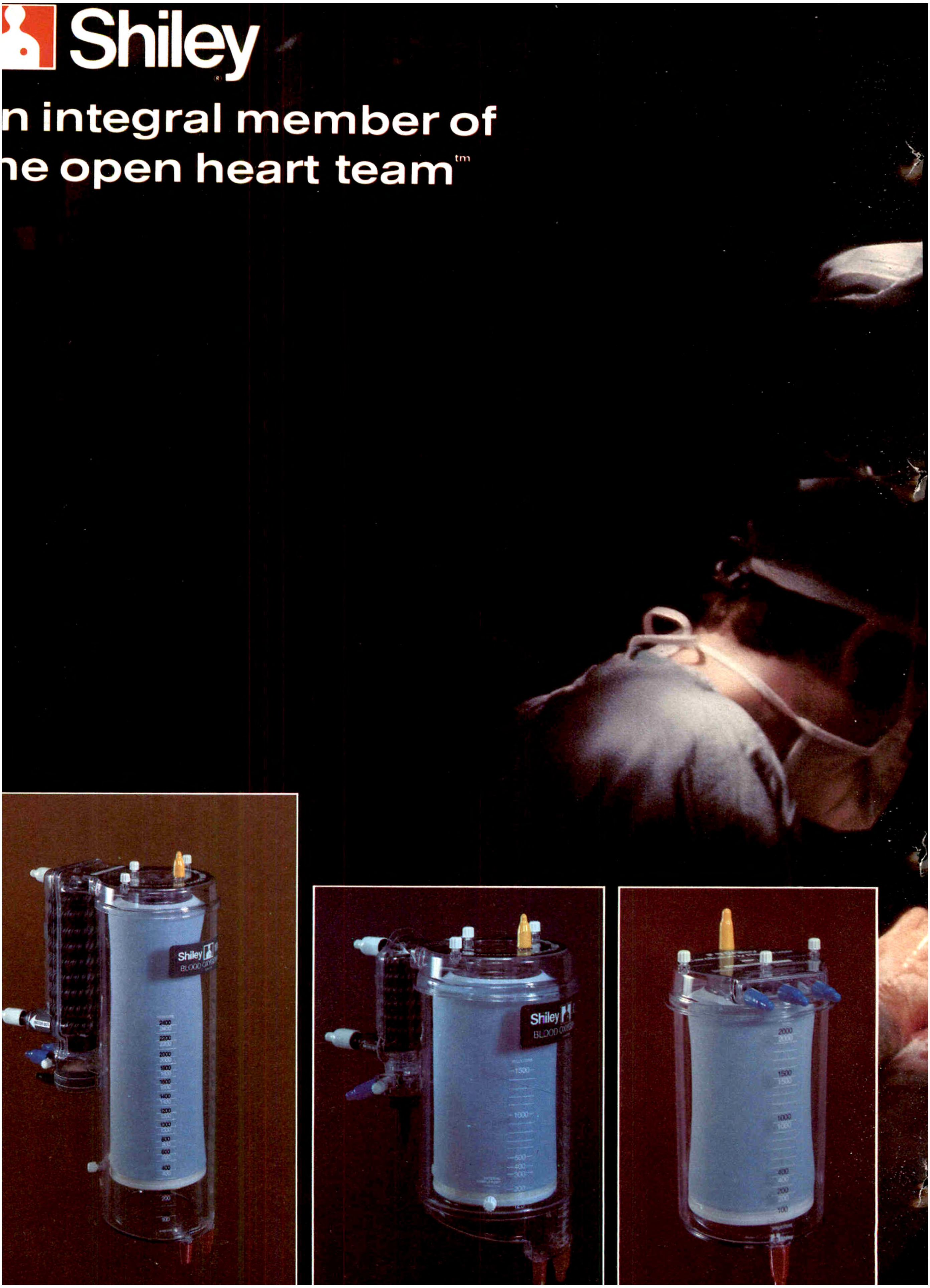
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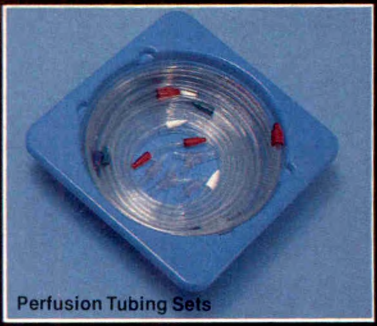

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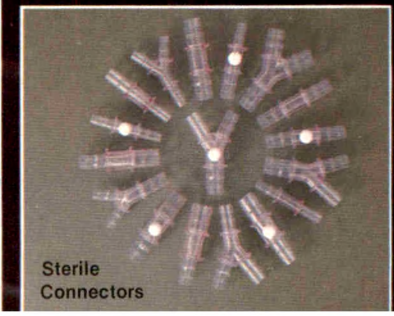

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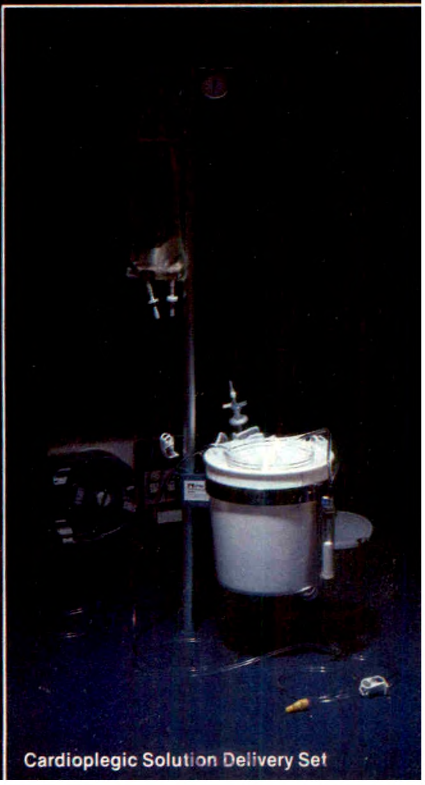

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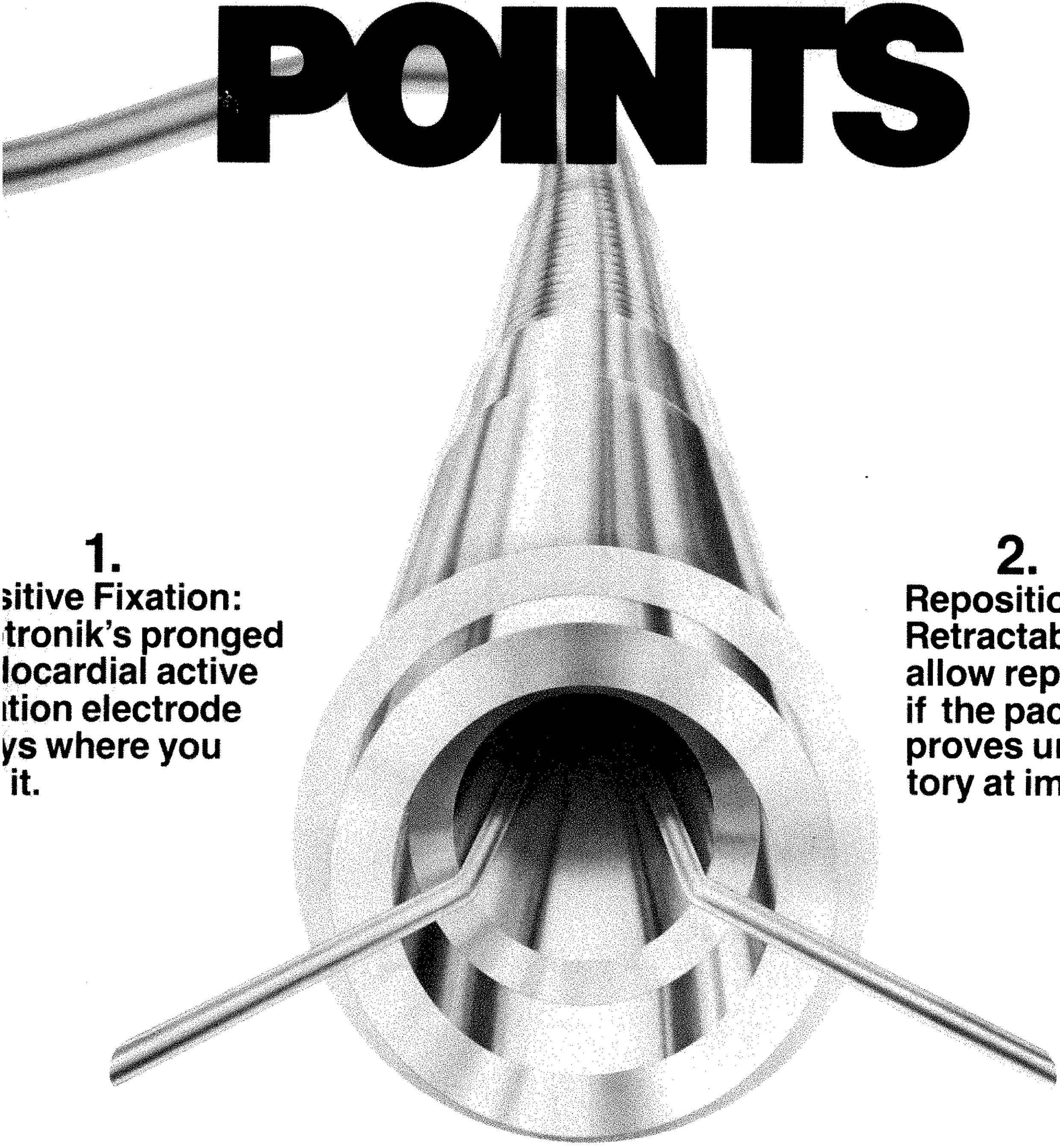

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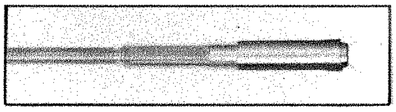

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Official Journal of The Society of Thoracic Surgeons
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Volume 30 Number 3 September 1980

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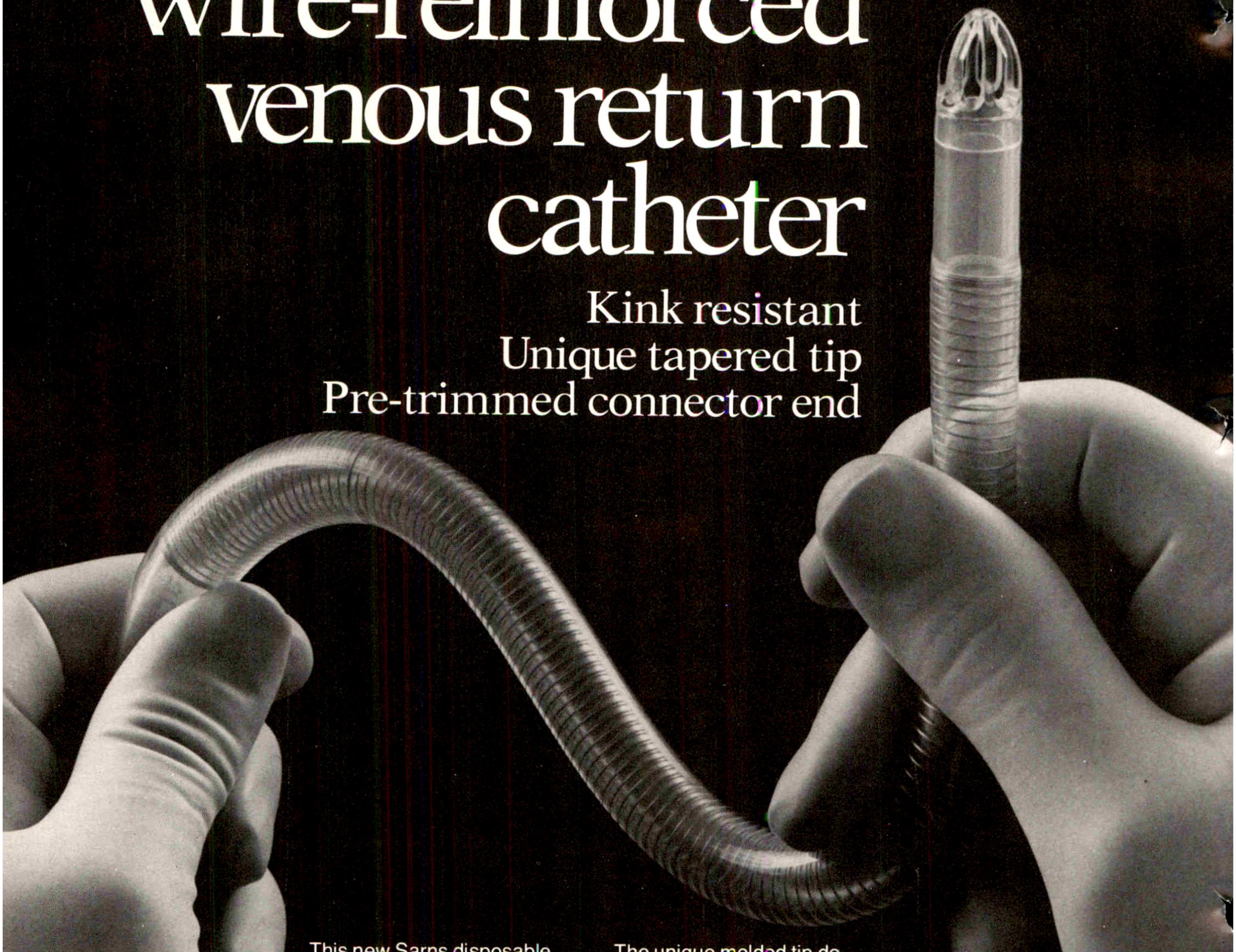

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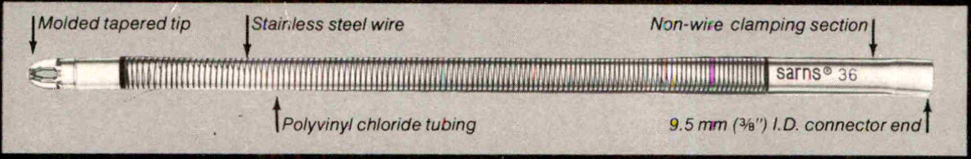
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Extended in vitro activity* against gram-negative organisms†: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, P. rettgeri, P. morganii, P. vulgaris,*† *Enterobacter,*† and *Haemophilus influenzae.*[1,2]

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‡Most strains of *Bacteroides fragilis* are resistant in vitro; however, infections caused by susceptible strains have been treated successfully.

§Tissue analysis gives primarily qualitative rather than meaningful quantitative data as to the presence or absence of an antibiotic in a particular body fluid or tissue. Therapeutic efficacy cannot be predicted by the level attained in a specific body fluid or tissue.

Note: Mandol should be given cautiously to penicillin-sensitive patients and is contraindicated in patients with known allergy to cephalosporins.

References:
1. Antimicrob. Agents Chemother., *9*:452, 1976.
2. Antimicrob. Agents Chemother., *8*:679, 1975.
3. Antimicrob. Agents Chemother., *8*:91, 1975.
4. Antimicrob. Agents Chemother., *9*:994, 1976.

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Urinary tract infections caused by *Escherichia coli*, *Proteus* species (both indole-negative and indole-positive), *Enterobacter* species, *Klebsiella* species, group D streptococci (*Note:* Most enterococci, e.g., *S. faecalis*, are resistant), and *S. epidermidis*

Peritonitis caused by *E. coli* and *Enterobacter* species

Septicemia caused by *E. coli*, *S. aureus* (penicillinase and non-penicillinase-producing), *S. pneumoniae*, *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae*, and *Klebsiella* species

Skin and skin-structure infections caused by *S. aureus* (penicillinase and non-penicillinase-producing), *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae*, *E. coli*, *Enterobacter* species, and *P. mirabilis*

Bone and joint infections caused by *S. aureus* (penicillinase and non-penicillinase-producing)

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Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefamandole. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

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Contraindication: Mandol is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY WITH MANDOL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

In newborn infants, accumulation of other cephalosporin-class antibiotics (with resulting prolongation of drug half-life) has been reported.

Precautions: Although Mandol rarely produces alteration in kidney function, evaluation of renal status is recommended, especially in seriously ill patients receiving maximum doses.

Prolonged use of Mandol may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

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Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Usage in Infancy—Mandol has been effectively used in this age group, but all laboratory parameters have not been extensively studied in infants between one and six months of age; safety of this product has not been established in prematures and infants under one month of age. Therefore, if Mandol is administered to infants, the physician should determine whether the potential benefits outweigh the possible risks involved.

Adverse Reactions: *Hypersensitivity*—Maculopapular rash, urticaria, eosinophilia, and drug fever have been reported. These reactions are more likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—Thrombocytopenia has been reported rarely. Neutropenia has been reported, especially in long courses of treatment. Some individuals have developed positive direct Coombs tests during treatment with the cephalosporin antibiotics.

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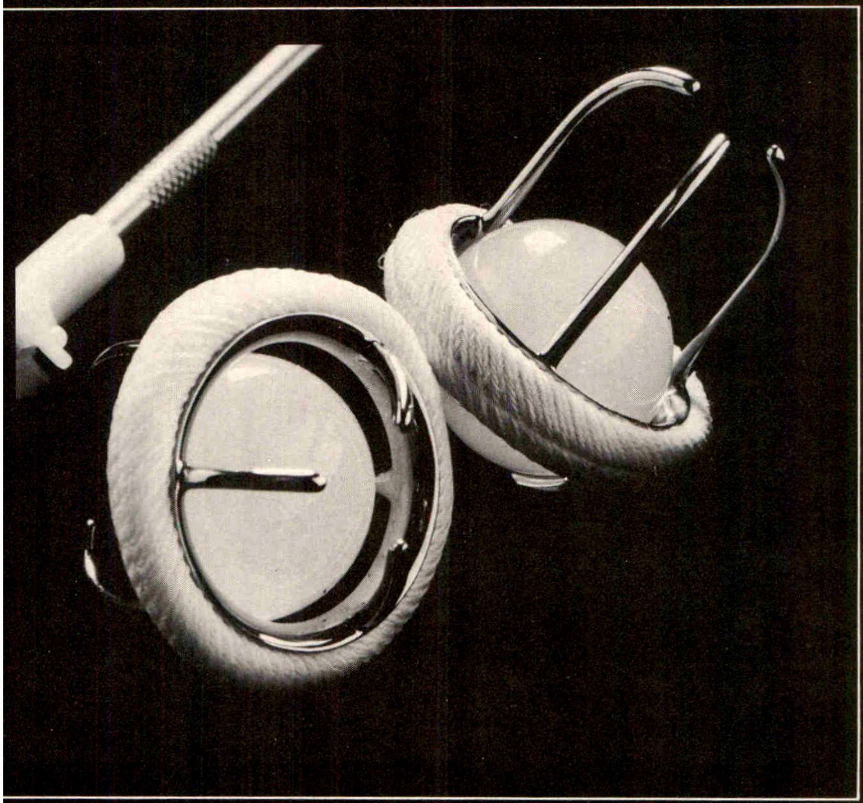

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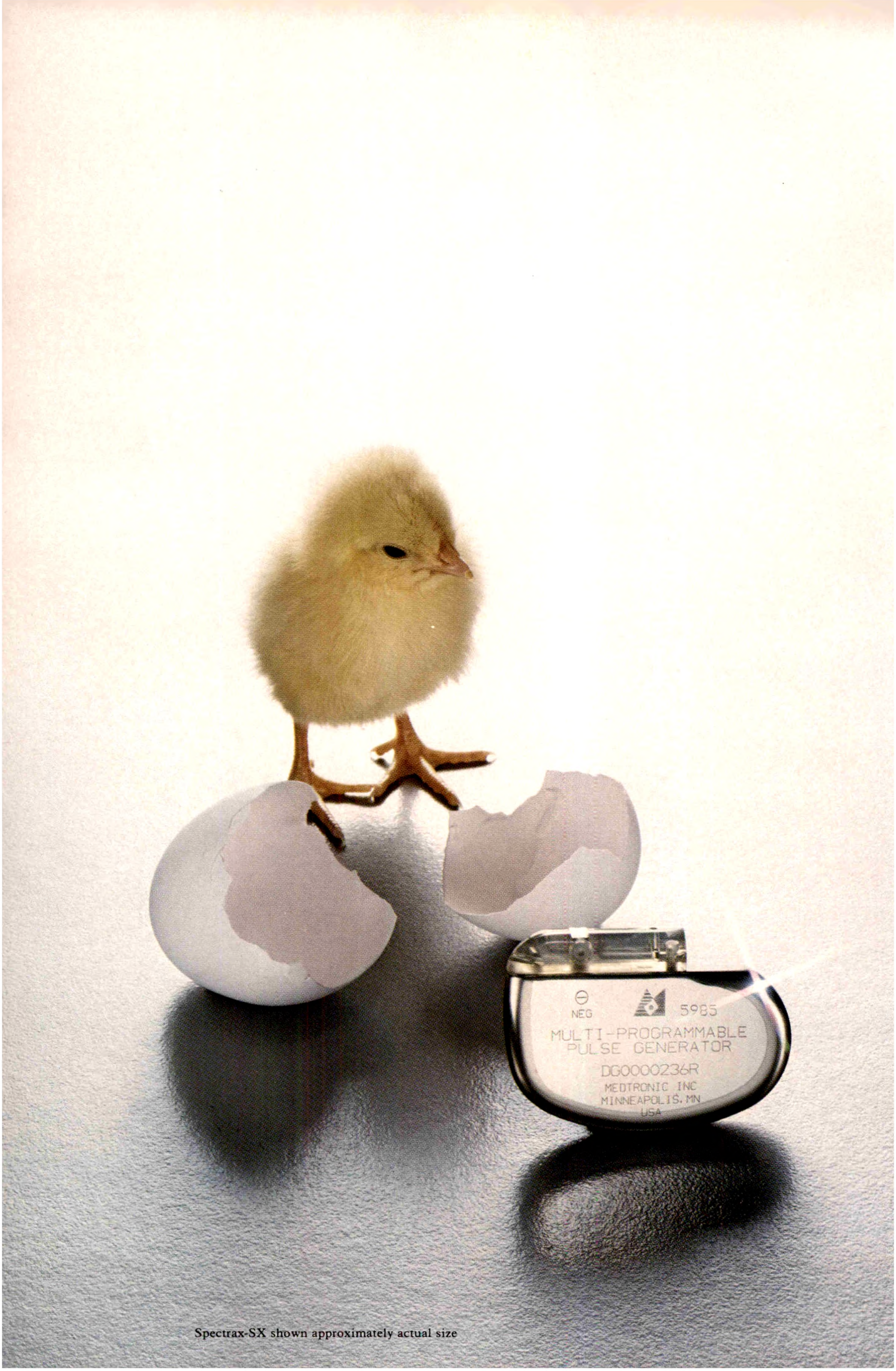

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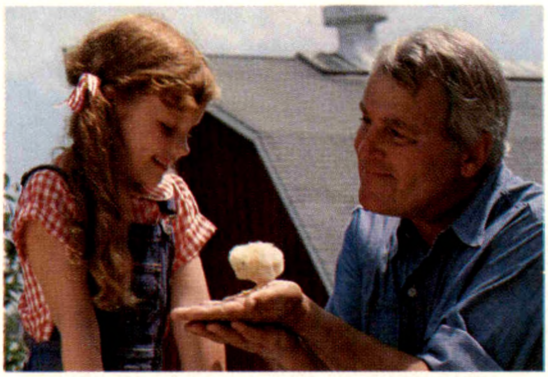

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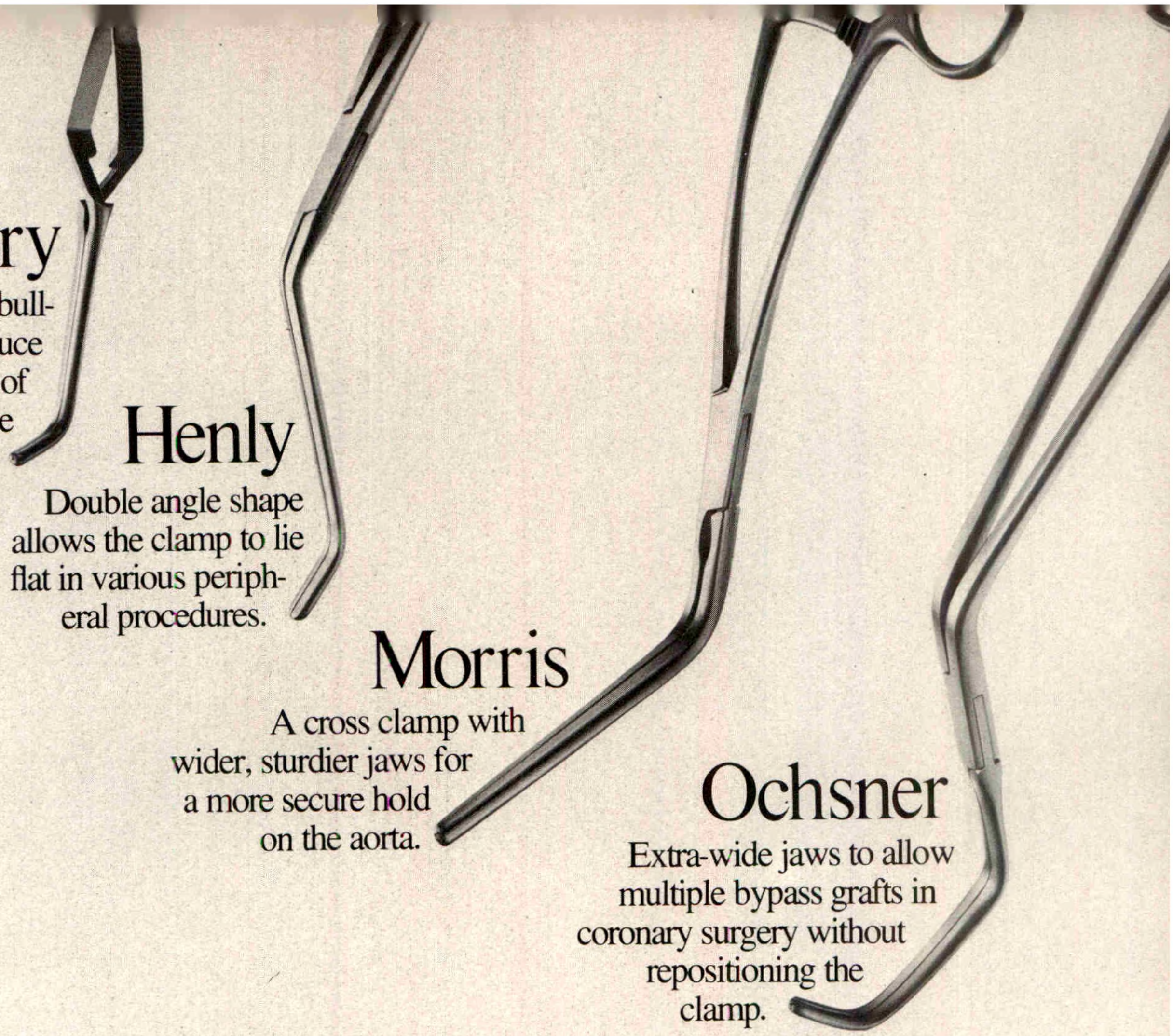

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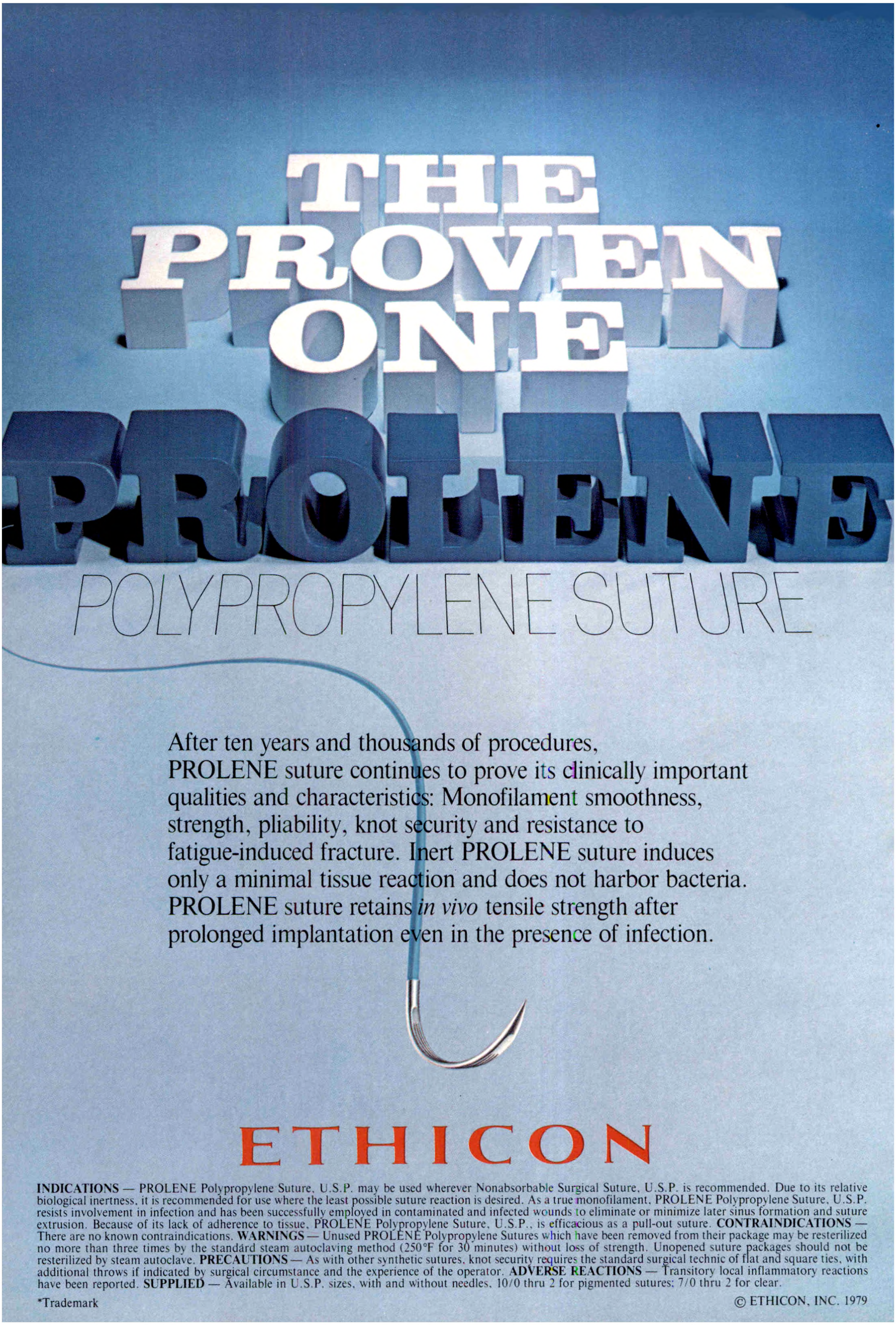

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EDITORIAL

Use of Mediastinoscopy in Selection of Patients for Lung Cancer Operations

F. Griffith Pearson, M.D.

The paper by Ashraf and co-workers "Selection by Mediastinoscopy and Long-Term Survival in Bronchial Carcinoma," which appears in this issue of The Annals (p 208), reports on an extensive experience with the use of mediastinoscopy in the selection for operation of patients with carcinoma of the lung. This paper is an extension of an earlier report by C. Nohl-Oser [1], a surgeon at Harefield Hospital, who was one of the pioneers in the use of mediastinoscopy following the original report of Carlens [2]. In the present report, the authors review their experience with 874 consecutive patients seen between February, 1966, and April, 1979. Except for the findings at mediastinoscopy, the preoperative evaluation in these patients indicated that all were presumably operable. Mediastinoscopy was used in all patients as a routine part of the preoperative assessment. If mediastinoscopy identified metastases in mediastinal lymph nodes, the patient was considered inoperable and resection was not tried.

Two hundred thirty-six patients (27%) in this series had positive superior mediastinal nodes identified at mediastinoscopy. None of these patients were treated by surgical resection, and the authors note that 79% were dead within a year of diagnosis and that only 4 patients (2%) lived for five years or longer. All 638 patients with negative findings at mediastinoscopy were operated on, and 620 patients (97.1%) underwent resection. Hospital mortality was 5.5%. Among the patients who had resection, the extent of lymph node involvement significantly influenced survival. Using Salzer's staging for lymph node involvement, Ashraf and colleagues report a 33% five-year survival for patients in Stage 0 or 1 (no nodal involvement or metastases restricted to intersegmental nodes), an 18.4% five-year survival in Stage 2 (nodal metastases restricted to interlobar or hilar nodes), and a 4% (2 of 53 patients) five-year survival in patients in Stage 3 (mediastinal nodes identified at the time of resection). In this latter group of 53 patients with positive mediastinal nodes, it is apparent that such involvement could not be identified at mediastinoscopy, and although the details of location are not given, it is probable that the mediastinal nodes in most of these patients were in locations not accessible at conventional mediastinoscopy (posterior subcarinal nodes, anterior mediastinal nodes, subaortic nodes).

In their introduction to this report, Ashraf and co-workers reviewed the controversy regarding the selection of therapy in patients with known involvement of superior mediastinal nodes. They point out that a number of centers consider mediastinal lymphatic involvement, *identified at mediastinoscopy*, to be a contraindication to surgical treatment. In contrast, other surgeons do not use mediastinoscopy as a routine method of preoperative assessment and do not consider involvement of mediastinal nodes as an absolute contraindication to surgical resection. The present report is "an attempt to clarify some of the points of dispute." In their conclusions, the authors note that the routine use of mediastinoscopy in patients with cancer of the lung, which is otherwise presumably operable, has almost eliminated the inoperable patients at thoracotomy.

No one can disagree with this observation. It is misleading, however, to note that the policy of witholding operation in patients with mediastinal node involvement *identified at mediastinoscopy* has not significantly modified the overall five-year survival rates. Ashraf and associates contend that the operative mortality in patients with involved mediastinal nodes

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actually exceeds the number of potentially long-term survivors, and state that this observation justifies their recommendation that patients with mediastinal lymphatic involvement should not undergo operation. This is a confusing and rather negative argument, and I believe that at the present time, there is a scanty, but gradually increasing body of evidence suggesting that some categories of patients with "mediastinoscopy positive" mediastinal nodes are best treated by surgical resection and adjuvant therapy. The following material summarizes a recent review of reported experience with patients who have lung cancer with mediastinal lymph node involvement who have been managed by resection.

There are five papers reporting survival data in patients with lung cancer involving mediastinal nodes *identified at the time of thoracotomy* and managed by resection without adjuvant therapy [3–7]. The five-year survival in these papers ranges from 0 to 29% (0, 0, 7%, 20%, 29%, respectively). In each review, the data regarding mediastinal node involvement were obtained from the operative record and the pathology report by retrospective chart analysis. None of the authors were able to identify the location of these mediastinal nodes; indeed, it can be assumed that the decision in many instances was made by the pathologist on receipt of the gross specimen. Furthermore, the survival data do not include patients with nonresectable lesions, or operative mortality. The great differences in survival identified in these five publications can logically be attributed, at least in part, to differences in the interpretation of what is or is not a mediastinal lymph node.

Three papers report survival in patients with positive mediastinal nodes *identified by mediastinoscopy* and subsequently managed by resection without adjuvant therapy [8–10]. There were no five-year survivors in any of these patients. Although the precise location of the involved mediastinal nodes is not identified, there can be no doubt that they were superior mediastinal nodes, which are accessible at mediastinoscopy.

Two publications present the results in patients with positive mediastinal nodes *identified at thoracotomy* and managed by resection and adjuvant therapy (postoperative radiotherapy, chemotherapy, or both) [6, 11]. In one of these papers, Naruke and co-workers [11] report a 19% absolute five-year survival in 64 patients managed by resection, followed in most cases by postoperative radiotherapy with or without the addition of mytomycin C. This is the only report in the literature that identifies precisely the location of the mediastinal nodes discovered at thoracotomy and subsequently resected. The survival figure of 19%, however, takes no account of those patients who had nonresectable tumors associated with superior mediastinal lymphatic involvement, no account of patients in this category who had "noncurative resections," and no account of operative mortality. The other report, by Kirsh and colleagues [6], records a 35% absolute five-year survival in 43 patients with squamous cell carcinoma and positive mediastinal nodes identified at thoracotomy, who were managed by resection and postoperative radiotherapy. These authors report an 11% absolute five-year survival in 45 patients with adenocarcinoma or large cell carcinoma and mediastinal nodes identified at thoracotomy, and managed by resection and postoperative radiotherapy. This again was a retrospective review which cannot identify the location of the involved mediastinal nodes, does not account for inoperable tumors or noncurative resections in such patients, and does not consider operative mortality in the survival statistics. Nevertheless, Kirsh and associates report *no* five-year survivors in a similar group of patients who were managed by resection alone.

I have reported previously on a group of patients with positive mediastinal nodes *identified at mediastinoscopy* and managed by preoperative irradiation and resection [12]. This experience was updated recently* and has data on 42 patients so managed. An absolute five-year survival of 9.5% was identified for all 42 patients. If one excludes from the 42 patients those who proved to have nonresectable lesions at thoracotomy, and the operative deaths, there remain 29 patients with an absolute five-year survival of 13.8%. If one restricts the review to those patients with squamous cell carcinoma who had resection at thoracotomy and excludes operative mortality, 20 such patients had an average survival of three years and an absolute five-year survival of 18.2%. The precise location of involved mediastinal nodes was recorded in each instance, and it again is emphasized that this represents a group of patients with mediastinal nodes that were identified by mediastinoscopy rather than thoracotomy.

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*Pearson FG, Cooper JD, Delarue NC, et al: Unpublished data, 1980.

Since mediastinoscopy was introduced to our Service in 1963 as a method of preoperative assessment in patients with lung cancer, we at Toronto General Hospital have continued to believe that some "mediastinoscopy positive" patients may best be managed by resection with adjuvant radiotherapy. Such patients are highly selected. At present, our criterion for selection is: ipsilateral mediastinal involvement of nodes, which from the findings at mediastinoscopy are judged to be completely resectable at subsequent thoracotomy. Nodal masses that are fixed to the trachea or aortic arch are a reason for exclusion, as is oat cell carcinoma.

In our original review [12] of 527 patients with presumably operable lung cancer who were evaluated by mediastinoscopy, there were 163 patients who were "mediastinoscopy positive." Of this group of 163 patients with metastases in mediastinal nodes, 32 (20%) were selected for combined treatment with preoperative irradiation and operation. The remainder were considered inoperable on the basis of the nature of the involvement identified at mediastinoscopy.

Although reports in the literature are scanty and prospectively collected data on the precise site of mediastinal nodes are almost nonexistent, our experience [12]* and that of Naruke [11], Kirsh [6], and their co-workers tend to support the contention that surgical resection with adjuvant therapy is advisable in selected instances. The most favorable results have been obtained in patients with squamous cell carcinoma. Almost all of the reports, however, indicate that resection and adjuvant therapy is rarely beneficial in patients with adenocarcinoma and large cell type. The management of these cell types by resection may be favorable if more effective adjuvant therapy becomes available in the future. It is obvious, however, that the present knowledge of the results of various therapies in patients with positive mediastinal nodes is too imprecise to permit any secure judgment or recommendation. It is imperative that all of us who have the opportunity to do so insist on methodical and prospective staging of the extent of mediastinal involvement by both preoperative and intraoperative evaluation. We also need an accepted international nomenclature defining the location of mediastinal nodes.

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*Pearson FG, Cooper JD, Delarue NC, et al: Unpublished data, 1980.

Selection by Mediastinoscopy and Long-Term Survival in Bronchial Carcinoma

M. H. Ashraf, F.R.C.S., P. L. Milsom, M.B.B.S., and R. K. Walesby, F.R.C.S.

ABSTRACT **In order to reduce the high rate of inoperability in patients with bronchial carcinoma, mediastinoscopy was carried out as a routine preoperative selection in 874 patients during 13 years. Two hundred thirty-six patients (27%) were found to have involved lymph nodes at mediastinoscopy and were not treated surgically. Follow-up data were available on 210 of them: 165 (79%) died within a year, 16 survived for 2 years, and 4 for 5 years. Pulmonary resection was carried out in 638 patients. Five-year survival in the series was 24.5% and 10-year survival (based on 104 eligible patients), 16.3%, including the operative mortality of 5.5%.**

Mediastinoscopy has not improved long-term survival to any great extent. However, it has raised the rate of resectability to 97.1% and lowered the operative mortality without denying the patient a chance of cure.

Selectivity has become an important consideration in the surgical management of patients with bronchial carcinoma, especially since there have been no advances in the treatment of this condition [2, 3, 21]. With the advent of lymph node biopsy by mediastinoscopy [8], many surgeons have changed their attitude toward the selection of patients for surgical treatment of bronchial carcinoma [19, 21, 23, 24]. Some consider mediastinal lymphatic involvement as found by mediastinoscopy to be a contraindication to operation because the 5-year survival rate in such patients is less than 10% [6, 9, 20, 22, 27, 28, 30]. Others, however, do not carry out mediastinoscopy as a routine preoperative investigation and therefore would not necessarily withhold surgical treatment in patients with bronchial carcinoma invading the mediastinal nodes [1, 13, 15, 25]. Selection by mediastinoscopy has provoked a widespread discussion among surgeons in recent years. This paper is an attempt to clarify some of the points of dispute.

Selection

All patients with bronchial carcinoma referred for surgical treatment to one thoracic unit at Harefield Hospital, London, underwent mediastinoscopy as a routine preoperative selection procedure beginning in February, 1966. When lymph nodes were found to be involved, no further surgical procedure was carried out. This policy was adopted on the basis of a previous investigation [16], which had shown the very poor 5-year survival of patients with bronchial carcinoma with mediastinal node involvement, even when treated by successful surgical resection. The long-term result of this policy is reviewed here.

Between February, 1966, and April, 1979, 874 patients with primary bronchial carcinoma were considered operable on clinical, roentgenographic, and bronchoscopic grounds. At mediastinoscopy, 236 patients (27%) were found to have involved mediastinal lymph nodes. They were not treated surgically. Six hundred thirty-eight patients underwent thoracotomy. All were staged at operation and later by histology using a surgical-pathological classification (Table 1) proposed by Salzer [26] in 1951 and modified by Nohl-Oser in 1962 [16], before the introduction of the TNM system.

Results

Follow-up data were available in 210 out of 236 patients with mediastinal node metastases who were excluded from operation. One hundred sixty-nine of the patients were men and 41 were women, a ratio of 4:1. They ranged from 47 to 78 years old. One hundred sixty-five patients

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We are grateful to Mr. H. C. Nohl-Oser for allowing us to use the records of his patients in this study and for valuable suggestions in the preparation of this paper.

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Table 1. Salzer's Classification (Modified)[a]

Extent of growth
A = Growth confined to the lung
B = Involvement of the visceral pleura, including interlobar fissure
C = Infiltration of the neighboring structures, e.g., parietal pleura, chest wall, esophagus

Lymph node involvement
0 = None
1 = Intersegmental nodes
2 = Interlobar or hilar nodes
3 = Mediastinal nodes

Vascular involvement
V = Demonstrable invasion of intima of the pulmonary veins

[a] The classification of Salzer [26], modified by Nohl [16].

(79%) died within a year, while 16 survived for 2 years and 4, for 5 years. The remaining 25 patients died at various times. Only the cutoff points are indicated.

The histology was as follows:

Squamous cell carcinoma	94
Oat cell carcinoma	71
Adenocarcinoma	14
Undifferentiated carcinoma	16
Anaplastic carcinoma	15

Of the 638 patients who underwent operation, a follow-up study from 1 to 13 years was possible in 608 (95%). There were 540 men and 68 women, a ratio of 9:1. They ranged between 34 and 81 years old. The majority of them were more than 60 years old (Fig 1), in comparison with the lower age in the series of Bignall and Moon [7]. This changing pattern of increase in age has also been remarked upon by other authors [4, 14].

There were 335 lobectomies and 255 pneumonectomies performed. In 18 patients the tumor could not be removed. Therefore the rate of resectability was 97.1%. Bronchopleural fistula occurred in 12 patients, an incidence of 2%. Of these patients, 9 died within a year while 3 survived for 4, 11, and 12 years. The overall hospital mortality was 5.5% with no noticeable difference between patients having total or partial resection of the lung.

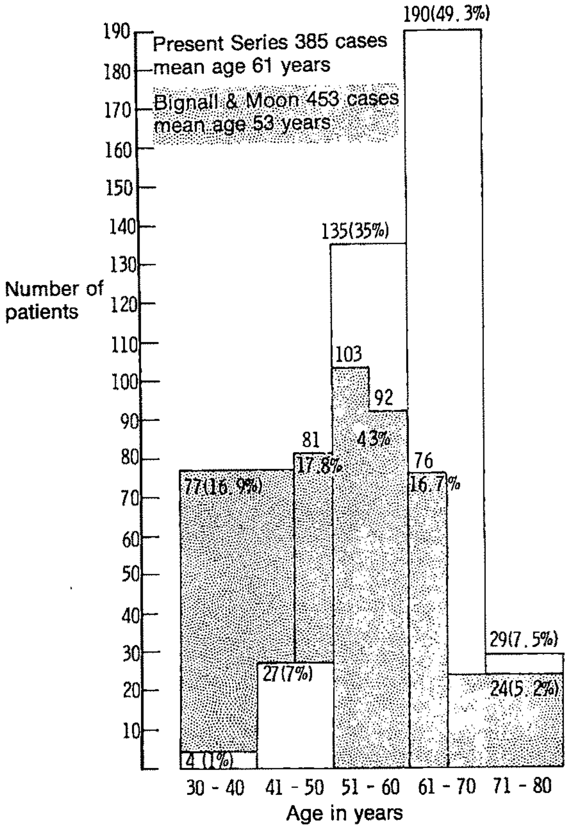

Fig 1. Age distribution of patients who had bronchial carcinoma with resectable lesions.

The hospital mortality has been included in the survival rate to allow comparison between surgical intervention and other forms of therapy that are known to carry a lesser mortality and morbidity. The value of the surgical-pathological classification is exemplified by analyzing 385 patients who had an operation before April, 1974. The extent of the primary growth has a definite influence on long-term survival (Fig 2). Out of 156 patients in Salzer's Stage A, 50 (32%) survived for 5 years in contrast to 40 out of 173 (23%) in Stage B and only 5 out of 56 (9%) in Stage C. The operative mortality was higher in the more advanced stages.

The importance of lymph node involvement was even more striking (Fig 3). Of the 218 patients with no lymph node involvement or in whom it was confined to intersegmental nodes (Stage 0 or 1), 72 patients (33%) were alive after 5 years, while 21 out of 114 (18.4%) survived when the interlobar nodes were involved (Stage 2) and only 2 patients out of 53 (3.7%) lived for 5

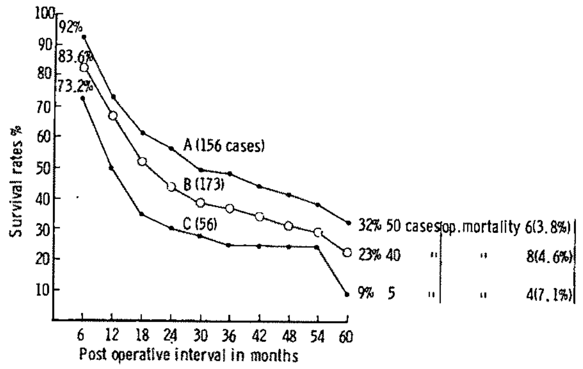

Fig 2. Influence of the extent of the primary growth on prognosis.

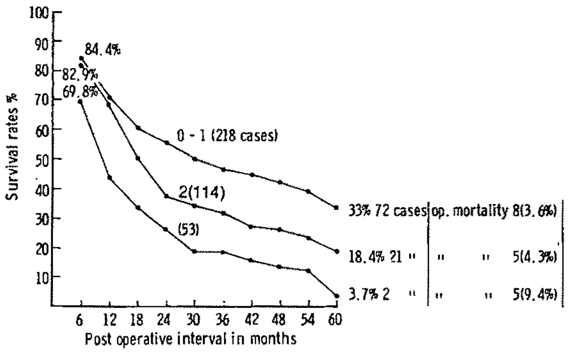

Fig 3. Effect of lymph node involvement.

years when the mediastinal lymph nodes were involved (Stage 3).

The histology of the tumor had a less striking influence on long-term survival compared with the two factors just mentioned. However, the majority of patients with squamous cell carcinoma and adenocarcinoma were confined to Stages 0, 1, and 2, while 43.3% of patients with oat cell carcinoma and 30.4% with undifferentiated carcinoma reached Stage 3 (Table 2).

The overall 5-year survival of the whole series is 24.5%, which includes the operative mortality. Ten-year survival was calculated for those patients who were operated on before April, 1969. Out of 104 eligible patients, 17 (16.3%) lived for 10 years. Fourteen of them had squamous cell carcinoma, and 11 were confined to Stages A and 0, signifying that the tumor was confined to the lung and the lymph nodes were not invaded.

Comments

On account of the high inoperability rate of 23 to 50% in patients with bronchial carcinoma [11, 12, 18, 29], Nohl-Oser [17] proposed mediastinoscopy prior to thoracotomy as a means of reducing unnecessary operations. A surgical-pathological staging was adopted for future assessment of surgical results. It is apparent from the result of this study that long-term survival is greatly influenced by the extent of the tumor and the lymph node involvement. The operative mortality increases threefold when the tumor progresses from Stage A to Stage C (see Fig 2) and actually exceeds the 5-year survival rate when the tumor spreads to the mediastinal lymph nodes (see Fig 3). The very poor survival at 5 years of 2 out of 53 patients (3.8%) with mediastinal lymph node involvement after operation (Stage 3) justifies, in our opinion, the policy of withholding surgical treatment in such instances.

In our series, the majority of patients with positive biopsy at mediastinoscopy not treated surgically died within 12 months but 4 survived for 5 years (mean survival, 11.7 months). On the other hand, in the series reported by Gibbons [10] all 93 patients with a positive biopsy at mediastinoscopy who had thoracotomy were dead within 2½ years (mean survival, 6 months). This shows once again the poor out-

Table 2. Influence of Histology on Lymph Node Involvement

	Stage of Tumor at Operation				
Cell Type	0	1	2	3	Total
Squamous cell carcinoma	81 (30.1%)	75 (27.9%)	86 (31.9%)	27 (10.0%)	269 (69.9%)
Adenocarcinoma	21 (42%)	11 (22%)	12 (24%)	6 (12%)	50 (12.9%)
Oat cell carcinoma	4 (13.3%)	4 (13.3%)	9 (30%)	13 (43.3%)	30 (7.8%)
Undifferentiated carcinoma	8 (34.8%)	3 (13.0%)	5 (21.7%)	7 (30.4%)	23 (5.9%)
Anaplastic carcinoma	10 (76.9%)	1 (7.7%)	2 (15.4%)	. . .	13 (3.4%)

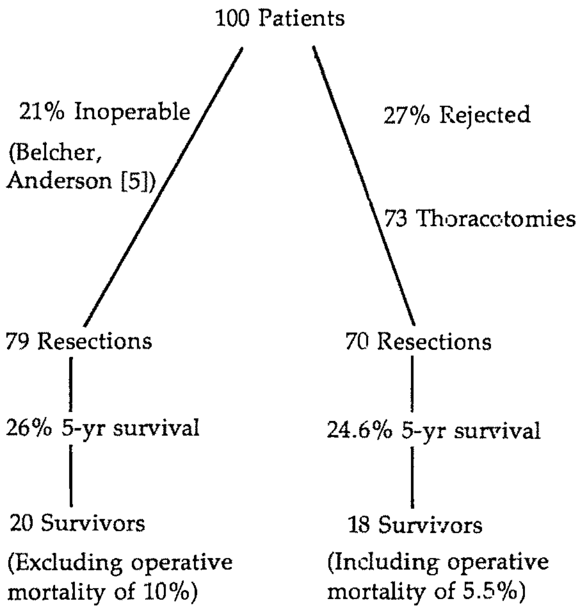

Fig 4. Results of conventional selection versus selection by mediastinoscopy in patients with bronchial carcinoma.

come of attempts to salvage patients with bronchial carcinoma invading the mediastinal lymph nodes. For example (Fig 4), we compared the 5-year survival of 100 patients suitable for pulmonary resection on clinical, roentgenographic, and bronchoscopic grounds. By conventional management, 100 thoracotomies would be performed with 79 resections possible [5]. With the stated 5-year survival of 26.5% following resection, 20 survivors are to be expected, but this excludes an operative mortality of 10%. In comparison, of the 100 patients who underwent mediastinoscopy, only 73 had a thoracotomy; 70 of these had a pulmonary resection. This resulted in a 5-year survival of 24.6% (18 patients) and in contrast includes the operative mortality of 5.5%. This illustrates that with the use of mediastinoscopy, 27 patients were spared unnecessary thoracotomy.

The following conclusions can be drawn from this study:

1. Any comparison of the treatment of bronchial carcinoma without staging is meaningless.
2. The routine use of mediastinoscopy has practically eliminated the inoperable patients at thoracotomy, without adversely affecting the overall 5-year survival.
3. Mediastinoscopy has resulted in higher resectability and lower mortality, even in elderly patients who today are considered for surgical treatment in increasing numbers.
4. The chances of long-term survival are meager when the tumor has invaded the mediastinal lymph nodes.
5. Selection by mediastinoscopy has not improved long-term survival. This tends to confirm that it is the biological behavior of the tumor that determines the ultimate prognosis rather than the selection. This and the fact that the operative mortality exceeds the long-term survival counters the argument that selection by mediastinoscopy denies some patients the chance of a cure.

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Discussion

DR. HERBERT SLOAN (Ann Arbor, MI): This was a beautiful paper, clearly presented as only the people in the British Isles can do. I agree with a great many things Dr. Ashraf has presented, but the major point of the discussion this morning has been that patients who have carcinoma of the lung with mediastinal metastases are not candidates for operation. From our experience, we simply could not disagree with this concept more. I will try to justify our own belief, which is that a patient who can undergo a resection in which all gross tumor is removed, including positive mediastinal nodes if they are present, can then undergo radiation therapy for the positive nodes. We believe that resection combined with postoperative radiation therapy in the presence of mediastinal nodes is valuable.

The numbers that we are talking about are not as extensive as those of Dr. Ashraf and his colleagues, but they extend from 1959 through 1972. Twenty percent of these patients who were resected had mediastinal metastases.

Our operative mortality is similar to that of Dr. Ashraf and his group. We believe that there is not very much difference between lobectomy or pneumonectomy.

Finally, what have we been able to achieve? Patients with squamous cell carcinoma who had mediastinal metastases and radiation therapy had a 30% 5-year survival. With adenocarcinoma it is a somewhat different story, but even here we had survivors for 5 years with adenocarcinoma and positive mediastinal nodes.

I do not know what the difference is between his group and ours. whether it is biology or geography or some other factor of which I am unaware, but I do think that we should address this problem and find some logical explanation for these differences and results both honestly arrived at.

DR. PAUL A. KIRSCHNER (New York, NY): The experience at the Mount Sinai Medical Center, New York, with mediastinoscopy as a routine staging modality before thoracotomy began in 1966 and thus duplicates the time period presented by Dr. Ashraf and colleagues. In our series of 475 patients, the male:female ratio is 1.7:1.0. But in the patients less than 60 years old, it is 1:1. This conforms to the current statistics that reveal the frighteningly rapid increase in incidence and deaths among women.

As regards cell type, we found that adenocarcinoma predominates, amounting to 48.6% of the total group. This differs from the material just presented. However, this phenomenon now has been observed in a number of published series. The most recent is the striking report from the Veterans Administration in which adenocarcinoma was found to be the most common cell type despite the almost exclusively male population [1]. I mention these two points because they represent biological features that have some effect on diagnosis, treatment, and prognosis.

Mediastinoscopy was positive in 44.6% of patients. We have considered a positive mediastinoscopy to be a contraindication to thoracotomy with but one exception—patients with limited disease who have been given preoperative radiotherapy and then undergo operation. In more than 33 patients, resectability is over 95% and survival at 5 years approximates 18% using the life table method. Also, most of the patients had adenocarcinoma.

Mediastinoscopy was positive in 35.9% of patients with adenocarcinoma, 38.6% of those with squamous cell, 72.5% of those with large cell undifferentiated, and 82.7% of those with oat cell carcinoma. The rate of resectability in the entire group of 475 was more than 92%. Operative mortality was 3.7% among the 268 patients who had resection.

Median survival in patients with mediastinoscopy alone was 6 months, exploratory thoracotomy only (15 patients), 9.2 months, and resection (268 patients), 48.7 months. Five-year survival for patients with adenocarcinoma was as follows: Stage I, 58%; Stage II, 30%; and Stage III (N2, T3, or both), 25%. In the case of squamous cell carcinoma, it was 70%, 43%, and 32%, respectively.

In conclusion, we agree with the speakers in advocating routine mediastinoscopy. Adherence to this policy will minimize the number of futile thoracotomies in what are "biologically inoperable" cases.

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DR. DONALD L. PAULSON (Dallas, TX): I believe we are all indebted to the presenters of this paper, particularly to Mr. Nohl-Oser. Really, this paper is a continuation of a long series of classic investigations into the anatomy of the lymphatic drainage of the lungs, studies that have contributed much to our knowledge of the spread of lung cancer.

The first investigation began in 1954 and extended through 1958 at the London Chest Hospital where Nohl-Oser examined carefully the operation specimens of lungs removed from a consecutive series of 211 patients. This study yielded valuable information regarding the location and peculiarities of the lobar drainage and lymphatic spread of bronchial carcinoma. The early findings were published in *Thorax* in 1956 and formed the rationale for our bronchoplastic procedures, particularly sleeve resection of the right main bronchus combined with a right upper lobectomy for bronchogenic carcinoma. The findings later were published in a monograph entitled *The Spread of Carcinoma of the Bronchus* in 1962. I would recommend these contributions as general reading for anybody interested in bronchogenic carcinoma.

Following the introduction of mediastinoscopy by Carlens in 1959, Nohl-Oser continued his studies. He scrutinized his early investigations by biopsy of paratracheal and superior tracheal bronchial lymph nodes and demonstrated the mediastinal spread of lung cancer. This was done in 749 patients, and the results were published later in many sources, particularly in the United States in Shields's book *General Thoracic Surgery*.

I would agree completely that the extent of the tumor and the stage of nodal involvement are basic to accurate staging of the lesion. Staging is based on accurate localization of involved nodes, which, of course, is essential to the surgical management of this disease.

In our experience, we have followed Nohl-Oser's excellent work on precise localization of the nodes involved. Lack of accurate localization leads to confusion. By careful staging in relation to the location of nodal involvement, our survival at 5 years was 45% for those with Stage 0 lesions using the Salzer classification, 30% for those with hilar or bronchopulmonary node involvement, and only 8% for those with Stage 3 or mediastinal node involvement.

I would not say that all patients with mediastinal node involvement are inoperable, but I believe careful selection is necessary. For instance, I would resect those with ipsilateral tracheobronchial nodes involved by squamous cell carcinoma after preoperative irradiation.

DR. RALPH J. LEWIS (New Brunswick, NJ): Since 1976, we have routinely utilized mediastinoscopy to stage carcinoma of the lung regardless of the size or anatomical configuration of the lesion. We have now done more than 2,000 mediastinoscopies and have had no mortality and a morbidity of less than 1%. Our rate of resectability has averaged 94%.

Initially, we carried dissection below the main stem bronchi. During the past 6 years, we have stayed above the main bronchus and have done biopsy on paratracheal nodes. We no longer believe that positive ipsilateral nodes below the main bronchus contraindicate surgical resection. Many thoracic surgeons have maintained that mediastinoscopy is not necessary since positive nodes can be removed at the time of thoracotomy. A sampling of our series has revealed that 11% of all patients undergoing mediastinoscopy have positive contralateral lymph nodes. These obviously cannot be removed.

As we are all well aware, many of our medical colleagues are now obtaining positive tissue from the lung using the flexible fiberoptic bronchoscope. They then rely on indirect studies, such as gallium scans or mediastinal tomography, to determine mediastinal lymph node metastases. When this is suspected, the patients are relegated to nonsurgical management. We have had an opportunity to do a mediastinoscopy on a number of these patients. In a large percentage of them, we found merely hyperplastic inflammatory lymph nodes free from tumor. We have been able to successfully resect these patients. I think thoracic surgeons should be on guard and not allow medical men to determine resectability on the basis of indirect studies.

I certainly enjoyed this presentation and agree with the authors' use of mediastinoscopy.

DR. ASHRAF: I thank the discussants for their comments. One point was raised by Dr. Sloan and Dr. Lewis—that positive mediastinoscopy is not necessarily a contraindication in their practice in patients with squamous cell carcinoma. I quote here a study carried out at London Chest Hospital in 1972 in which 93 patients with bronchial carcinoma had a positive result at mediastinoscopy. The surgeons were not informed of this, and all patients underwent thoracotomy. With a very high inoperability rate, they all died within 2½ years. Mean survival was only 6 months. That put many surgeons off operating on patients with positive mediastinoscopy.

An important observation we made in our study is that the operative mortality is three times higher when the mediastinal nodes are invaded. It is 9%, while the 5-year survival of those patients is only 3.7%. Therefore, we did not think it justified to operate on patients with bronchial carcinoma with invasion of mediastinal nodes. There may be geographical factors contributing to the severity and distribution of the disease which also determine the management. However, I have given you our results in England as stated for the years 1966 to 1978.

Notice from the Southern Thoracic Surgical Association

The Twenty-seventh Annual Meeting of the Southern Thoracic Surgical Association will be held at The Greenbrier, White Sulphur Springs, WV, Nov 13–15, 1980. There will be a $100.00 registration fee for nonmember physicians except for guest speakers, authors and co-authors on the program, and residents. There will be a Postgraduate Program on Selected Operations by Experts. This meeting has been approved for Category I, 14 hours CME credit.

The Scientific Program appears at the end of this issue of *The Annals of Thoracic Surgery* (pp 304–306). Manuscripts of papers accepted for the program must be submitted to *The Annals of Thoracic Surgery* by October 15, 1980.

Hotel reservations are sent to members. Guests may correspond with The Greenbrier, White Sulphur Springs, WV 24986. (Phone: (304) 536-1110.)

Occult Carcinomas of the Lung

Nael Martini, M.D., and Myron R. Melamed, M.D.

ABSTRACT **In 1974, we reported 26 patients with roentgenographically occult lung carcinomas. In 13 (50%) of them, the tumor was localized and treated by resection while the disease was still early (Stage I). These patients have done well, and the median survival has reached 8 years. We have added 21 patients to the series since our last report. Localization was by fiberoptic bronchoscopy in all 21. Fourteen of these patients had Stage I disease and were treated by resection.**

Of a total of 27 patients with early disease treated by resection, none has had recurrence after follow-up extending from 2 months to 20 years. However, in 21 of the entire 47 patients (45%) a second carcinoma developed, 15 (71%) of which were second lung carcinomas.

Occult carcinomas of the lung are detected by sputum cytology in patients who have no evidence of disease on routine chest roentgenograms. However, the presence of cancer cells in sputum does not necessarily imply that a tumor is in the lung or bronchus as opposed to the upper airways, nor does it imply an early carcinoma. Nearly 30% of patients with positive sputum and roentgenographically occult lesions will be found to have cancers of head and neck origin. Only when the tumor is found and resected, and its extent histologically assessed can one state with confidence that an early, potentially curable carcinoma is present.

From 1947 to 1979, 47 patients with occult lung carcinomas were seen and treated at our center. Of these, 26 were reported in 1974 [6] and 21 have since been added to the study. Based on this experience, we will discuss features of importance in the behavior and management of occult carcinomas.

Material and Methods

From 1947 to 1979, 54 occult lung carcinomas were seen in 47 patients. Thirty-two patients had a single occult cancer; 8 had 2 carcinomas of the lung, 1 of which was occult; and 7 had 2 separate occult lung carcinomas.

There were 46 men and 1 woman ranging from 39 to 75 years old with a median age of 63 years and an average age of 59 years. Most patients were in the sixth and seventh decades.

One patient never smoked. Four had not smoked for from 6 months to 15 years, and 41 patients had smoked one or more packs of cigarettes a day for at least 20 years. One patient had a pleurectomy for asbestosis 20 years prior to the development of the lung carcinoma, and 11 workmen may have been exposed to carcinogens through their occupation. These were a longshoreman, a painter, a cobbler, a hat blocker, two laundry operators, a bookbinder, a sheet metal worker, an aircraft assembler, a steel construction worker, and a plasterer. Twenty-four cancers were detected on cytological sputum examination in healthy individuals without symptoms (Table 1). Hemoptysis was present in 17 of 23 patients with chest symptoms. The final diagnosis was adenocarcinoma in 5 patients and epidermoid carcinoma in 49 tumors in 42 patients. The location of the tumor was in a lobar or main bronchus (central) in 22 patients and in a segmental or subsegmental bronchus (peripheral) in 25 (Figure). Whereas 30% of the tumors in the earlier series were peripheral, 80% of the recently reviewed tumors were peripheral in location.

Method of Localization

A head and neck examination was carried out in all patients whose tumor was detected on a sputum cytology examination in the absence of symptoms. This examination was performed by a head-and-neck surgeon and included indirect

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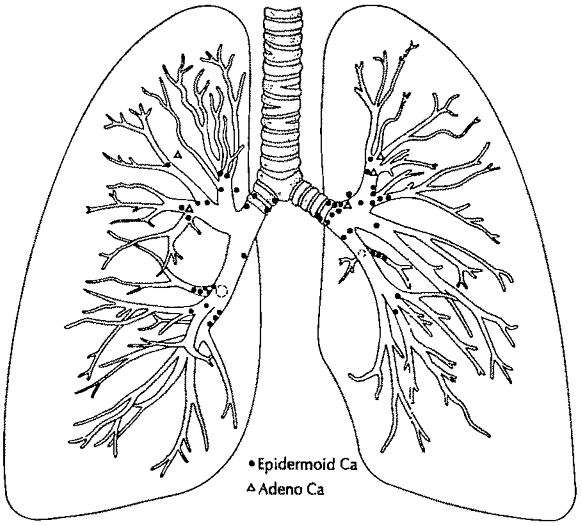
Table 1. Presenting Symptoms at Detection in 47 Patients

Symptoms	1974 Series	Recent Patients	Total
None	7	17	24
Hemoptysis	14	3	17
Wheezing	...	1	1
Hoarseness	1	...	1
Chest pain, cough	4	...	4
Total	26	21	47



Location of 54 lesions in 47 patients.

and direct laryngoscopy. When no abnormality was found in the upper airways, bronchoscopy was performed. If the tumor was seen at bronchoscopy, bronchial washings and brushings as well as bronchial biopsy were obtained to confirm the localization. When the tumor was not visible, a careful inspection of the entire tracheobronchial tree was carried out. This included visualization of all lobar and segmental bronchi up to and including fifth and sixth generation bronchi. Systematic brushing of each segment and subsegment was carried out. All specimens were labeled carefully, and cross-contamination was avoided. The number of cytological samples ranged from thirty to forty-five specimens. All bronchoscopies were performed under general anesthesia with endotracheal intubation since many necessitated one to two hours. When initial localization attempts were unsuccessful, reexamination was recommended at intervals of eight to twelve weeks with sputum examinations at intervals of two to four weeks.

A positive bronchoscopic biopsy was considered adequate for localization. If no lesion was visible, localization by cytology was accepted only when selected brushings from a given site were positive on two separate examinations.

The rigid bronchoscope was used in most of the 26 patients in the 1974 series. As a result, bronchoscopic localization was successful in only one-half of the patients, and localization was by selective bronchography in 11 patients. Four patients were surgically explored with what is now believed to have been inadequate evidence of localization, with negative findings.

Since the advent of the flexible fiberoptic bronchoscope, bronchoscopy has been our only method of localization and bronchograms have not been necessary. Of 25 occult carcinomas in the more recent years (21 new lesions and 4 second occult lesions), all were localized by bronchoscopy while the chest roentgenogram was still normal. No thoracotomy has been performed without precise localization of the tumor.

Of 54 occult lung carcinomas, 40 (74%) necessitated one bronchoscopy and 14 required two or more bronchoscopic attempts to localize the source of cancer cells. Five patients seen in the last 5 years underwent more than one bronchoscopy; 2 required four bronchoscopies before firm evidence of localization was obtained, and both had peripherally located, in situ carcinoma without invasion. The bronchial mucosa in 1 patient appeared entirely normal with no grossly visible lesion in the resected specimen even under inspection with a hand lens at 10× magnification. He had a limited area of carcinoma in situ that was defined after step sectioning of the entire resected bronchial tree.

Stage of Disease at Treatment

Although all patients seen had roentgenographically occult carcinomas, the stage of disease at presentation varied (Table 2). Thirty-three had Stage I disease and 14, Stage II or III disease. We have defined early carcinomas to be tumors classified as Stage I at treatment and

Table 2. Stage of Disease at Treatment

Stage	No. of Patients	
Stage I	28	
TIS N0 M0		6
T1 N0 M0		16
T1 N1 M0		3
T2 N0 M0		3
Stage II	1	
Stage III	13	
T3 N0 M0		4
T3 N1 M0		3
T3 N2 M0		1
T1 N2 M0		3
T1 N0 M1		1
T3 N0 M1		1
Stage I (Clinical)	5	
Total	47	

advanced carcinomas as Stage II or III at treatment, in accordance with the American Joint Committee for Cancer Staging and End-Results Reporting.

Results

Treatment and Survival

In 1974, we reported 26 patients with roentgenographically occult lung carcinomas. Of these, 8 had advanced disease at the time of localization and treatment; 5 were presumed to have early disease, but 2 refused treatment and 3 had external irradiation. All 13 patients have since died of the disease. Survival ranged from 5 to 42 months, with a median survival of 15 months and an average survival of 18 months.

In 13 of the 26 patients (50%), the tumor was localized and treated by resection while it was still at an early stage. The average survival had reached 9 years as of this writing and median survival, 8 years (Table 3). One patient treated in 1960 died postoperatively of an empyema and bronchopleural fistula without residual tumor at postmortem examination. Twelve lived from 2 to 20 years, including 5 who are alive and well after 8 to 20 years. One patient is alive at 9 years with a second lung carcinoma; 6 have died of other causes 2 to 17 years later. The causes of death were myocardial infarction in 2 patients, pneumonia in 1, an uncontrolled second lung carcinoma in 2, and a pharyngeal carcinoma in 1.

Six of 21 patients with occult lung carcinoma seen since the last report had advanced disease despite prompt localization (Table 4). Five died of the carcinoma 9 to 30 months after treatment (median survival, 15 months). One patient was treated recently and is alive with disease at 1 month.

Fourteen of the 21 patients (67%) had Stage I disease and were treated by resection. Five had only in situ carcinomas. Thirteen of the 14 are alive, 11 free from disease and 2 with new carcinomas, 1 in the lung and 1 of the biliary tract (Table 5). One patient died of carcinoma of the pancreas at 50 months. Although the median survival to date in this group of patients is 46 months, the follow-up is still short.

One additional patient with clinical Stage I disease has severe diffuse obstructive emphysema precluding surgical resection. He has a peripheral epidermoid carcinoma located in a subsegmental bronchus, believed to be in situ or focally invasive, and was treated by endoscopic electrocoagulation. He is alive with persistent disease at 33 months, and chest roentgenogram is still normal.

In 7 patients with early occult lung carcinomas treated by resection, a second occult lung cancer developed. Two of them underwent resection when the disease was early, and both patients are alive and well. One other patient had advanced disease at operation and has since died of the disease. Four received external irradiation to avoid further compromise of lung reserve by excision. One died of a myocardial infarct 2½ years after irradiation with no evidence of residual cancer at postmortem examination. One died of the disease, and 2 are alive with disease. The period of follow-up in all 7 patients is short, ranging from 8 to 30 months.

Of a total of 27 patients with early lung cancer treated by resection from 1949 to 1979, none has had recurrence of the original tumor after follow-up extending from 2 months to 20 years.

Multiple Carcinomas

Two separate primary cancers were identified in 21 of the 47 patients (45%). Fifteen patients (32%) had a second lung cancer, 7 of which were second occult carcinomas (Table 6).

Table 3. Outcome for 13 Patients with Potentially Curable Carcinomas Treated by Resection (1947–1972)

Patient No.	Present Status: Alive	Present Status: Dead	Survival (yr)	Cause of Death	Remarks
1	x	...	16	NA	No evidence of disease
4	x	...	20	NA	No evidence of disease
14	x	...	8	NA	No evidence of disease
16	x	...	9	NA	No evidence of disease
17	x	...	11½	NA	No evidence of disease
15	x	...	9	NA	Second lung cancer 8 yr later; treated by external radiation therapy
2	...	x	0	Empyema/bronchopleural fistula	No residual cancer at postmortem examination
25	...	x	6	Pneumonia	No tumor at postmortem examination
6	...	x	17	Myocardial infarct	Second lung cancer 12 yr later, also resected; no residual cancer at postmortem examination
13	...	x	4½	Myocardial infarct	Second lung cancer 2 yr later, treated by external radiation therapy; no residual cancer at postmortem examination
3	...	x	6	Other cancer	Second lung cancer 5 yr later
18	...	x	7	Other cancer	Second lung cancer 5 yr later
24	...	x	2	Other cancer	Uncontrolled cancer of pharynx and gum (postmortem examination)

NA = not applicable.

Table 4. Survival in 6 Patients with Stage II and Stage III Lung Carcinoma Seen Between 1973 and 1979

Patient No.	Treatment	Stage	Present Status: Alive with Disease	Present Status: Dead	Survival (mo)	Remarks
27	Pneumonectomy	T2 N1 M0	...	x	20	Local recurrence and distant metastases (postmortem examination)
38	Pneumonectomy	T3 N0 M0	...	x	15	Second lung cancer treated by implant; died of second cancer
43	Lobectomy	T3 N1 M0	...	x	9	Epidermoid cancer of larynx in 1972; occult adenocarcinoma 5 yr later; died of metastases to bone and liver (postmortem examination)
44	None	T3 N0 M0	...	x	9	Seen with left hilar mass, diagnosed as oat cell carcinoma after resection; had simultaneous keratinizing diffuse epidermoid carcinoma of right bronchus
45	Lobectomy	T1 N2 M0		x	30	Extensive local recurrence (adenocarcinoma of lung)
47	Thoracotomy, implant	T1 N2 M0	x	...	1	...

Table 5. Survival in 15 Patients with Stage I Lung Carcinoma Seen Between 1973 and 1979

Patient No.	Treatment	Pathology		Present Status			Survival (mo)	Cause of Death	Remarks
		In situ	Invasive	Alive/ Well	Alive/ Disease	Dead			
28	Lobectomy	x	x	x	...	...	63	NA	Late localization (12 mo)
29	Lobectomy	x	x	x	...	...	54	NA	Second occult lung cancer 4 yr later; also resected
30	Lobectomy	x	x	...	...	x	50	Cancer of pancreas	Cancer of pancreas 3½ yr later; no lung recurrence
31	Lobectomy	x	...	...	x	...	56	NA	Adenocarcinoma of biliary tract 3 yr later; no lung recurrence
32	Lobectomy	x	x	x	...	...	55	NA	...
33	Pneumonectomy	x	x	...	x	...	50	NA	Second occult lung cancer 3½ yr later; treated by radiation therapy
34	Lobectomy	x	...	x	...	...	46	NA	Late localization (13 mo)
35	Lobectomy	x	...	x	...	...	46	NA	...
36	Lobectomy	x	x	x	...	...	38	NA	Second occult lung cancer 1 yr later; also resected by lobectomy
37	Lobectomy	x	...	x	...	...	38	NA	Late localization (17 mo)
40	Lobectomy	x	x	x	...	...	24	NA	...
41	Lobectomy	x	x	x	...	...	7	NA	Had prior lobectomy for Stage I lung cancer; occult lung cancer 3 yr later
42	Lobectomy	x	...	x	...	...	7	NA	Had prior resection for Stage I adenocarcinoma of lung; occult lung cancer 4 yr later
46	Lobectomy	x	x	x	...	...	2	NA	...
39	Bronchoscopic cauterization	x	...	...	x	...	33	NA	Severe obstructive pulmonary disease precluding resection

NA = not applicable.

Table 6. Incidence of Multiple Cancers in 47 Patients

Type	Before	Simultaneous	After	Total
Lung	5	1	9	15(32%)
Tongue	1	...	...	1
Larynx	1	...	...	1
Pharynx	...	...	1	1
Pancreas	...	...	1	1
Common duct	...	...	1	1
Sarcoma of chest wall	1	...	...	1
Total	8	1	12	21/47 (45%)

Twenty-six patients with early lung carcinoma had had a follow-up of at least 2 years at our center (13 from the early study and 13 from the subsequent group). Thirteen of the 26 (50%) had 2 cancers; 10 of these 13 patients had 2 lung cancers (10 out of 26 or 38%) and 7 of these (7 out of 26 or 27%) had 2 separate occult lung carcinomas. The interval between 2 carcinomas has ranged from a synchronous presentation to 30 years in 1 patient whose initial tumor was a neurogenic sarcoma of the chest wall. The median interval between 2 cancers was 3½ years (less than a year in 2 patients, 1 to 3 years in 7, 3+ to 5 years in 6, and more than 5 years in 6).

Comment

Roentgenographically occult carcinomas represent a very small group of lung cancers (less than 0.5% of all lung cancers). By definition, they are detected on sputum cytology examination when the chest roentgenogram is normal. In our 1974 series, the majority of patients were seen initially with hemoptysis [5, 8, 10, 12]. Flexible bronchoscopy was not available, and localization with the rigid bronchoscope was not always successful. In many instances, treatment was delayed until the tumor became visible on chest roentgenograms.

In 1974, we embarked on a national lung cancer detection program and began screening 10,000 cigarette-smoking men 45 years old or older with periodic sputum cytology examination and chest roentgenograms [9, 11]. The majority of the patients in the latter series have come from this screening program and have been asymptomatic. Also, the fiberoptic bronchoscope has become our main diagnostic tool [3, 4, 13]. When done carefully, localization by bronchoscopy is possible in virtually every instance. Bronchograms for additional evidence of localization have not been necessary, and no thoracotomy has been performed without clear evidence of the precise location of the tumor.

When the lesion is visible at bronchoscopy, localization is no longer a problem. However, when the lesion is not seen, a careful inspection of the entire tracheobronchial tree becomes necessary with systematic brushing of all segments and subsegments. This is often a tedious and time-consuming procedure, requiring fiberoptic bronchoscopy under general anesthesia [3, 4, 13].

With experience, we have acquired sufficient confidence in endoscopic localization to make the following statement: If all cytological specimens obtained at bronchoscopy are negative, for practical purposes lung carcinoma is excluded as the source of the positive sputum cytology. In 1 such patient, after a negative head and neck examination, three bronchoscopies were done to localize the source of the occult carcinoma. All cytological material obtained at bronchoscopy failed to demonstrate tumor, but the sputum examinations were persistently positive. A carcinoma of the tongue was finally identified as the source of the positive sputum.

Mediastinoscopy has little value in occult tumors. The use of hematoporphyrin, of tantalum bronchography, and more recently of computerized chest tomography is under investigation but they have shown no benefit thus far.

Most of the roentgenographically occult but advanced carcinomas were epidermoid and central in location, and hidden by mediastinal shadows. Of interest is the fact that 5 patients with adenocarcinoma also were seen at an occult stage and all had advanced disease at treatment. Four of the 5 had peripheral bronchoalveolar carcinomas and in 3, localization was delayed. The fourth patient was seen with hemoptysis, and an adenocarcinoma, bronchiolar type, was identified visually and confirmed by bronchoscopic brushings of a subsegment of the posterior segment of the left upper lobe. At thoracotomy, the tumor diffusely involved 1.5 cm of lung parenchyma on the mediastinal aspect of the left upper lobe. Pleural washings at thoracotomy showed free cancer cells present, and within 4 months the patient had diffuse bone metastases. The fifth patient had an endobronchial papillary adenocarcinoma in a segmental bronchus; he had mediastinal lymph node metastases, not visible on chest roentgenograms.

Also of interest is the fact that in patients with epidermoid carcinoma, tumor growth was generally slow. Early carcinoma was demonstrable in many instances despite delay in localization and treatment.

Of importance is the fact that only patients with early disease treated by excision have done well and lived for a long time. In contrast, patients with presumed early disease treated by other means have done poorly. Theoretically, the in situ and superficially invasive epidermoid carcinomas of a major bronchus should be amenable to ablative local treatment. However, in 1 patient who could not withstand lobectomy, we treated an area of in situ carcinoma by endoscopic cautery. Although the disease was controlled temporarily, it has recurred. It is to be hoped that new methods of treatment for this type of patient will be developed in the coming years.

From a pathological standpoint, occult epidermoid carcinomas are generally in situ and superficially invasive tumors confined to the bronchial wall [14, 15]. Some are limited lesions; others extend over great distances along the bronchial mucosa [1, 2]. Despite this, if the margin of resection is free from tumor, there is no recurrence. In the 1974 series, 2 patients had in situ carcinoma at the resected margin and were treated by external irradiation, without further recurrence. Two others had invasive carcinoma at the resected margin, and both died of persistent disease despite treatment. In the more recent group of patients with potentially curable occult carcinoma, 12 were treated by lobectomy and 1 by pneumonectomy; no residual carcinoma was seen at the resected margin in any patient.

From the present study we can conclude the following:

1. The vast majority of occult carcinomas are epidermoid cancers. In our series, 91% were epidermoid carcinomas and 9% were adenocarcinomas.
2. A patient seen with positive findings on sputum cytology and a normal chest roentgenogram does not necessarily have a lung cancer but may have a head and neck carcinoma.
3. If the cancer source is a lung and if the cell type is an adenocarcinoma, the tumor is likely to be advanced and probably incurable. However:
4. If the cell type is epidermoid carcinoma, at least 2 out of 3 patients will have an early cancer at treatment and will be cured of the disease if resected.
5. Because of an anticipated long survival, patients with occult carcinoma remain at risk to have a second cancer [7], usually an airway carcinoma.
6. Localization by fiberoptic bronchoscopy is possible in nearly all instances.

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Discussion

DR. PETER C. PAIROLERO (Rochester, MN): I congratulate the authors for a timely and thorough presentation of occult lung cancer. However, I think it is important to remind the Society again that the definition of occult cancer, namely, positive sputum cytology and negative chest roentgenogram, does not necessarily imply occult lung cancer. In addition, this definition gives no clue as to the stage or the cell type of the neoplasm.

Since 1971, the Mayo Lung Project has evaluated 75 patients with occult cancer. Eight patients, or 11%, were found to have upper airway cancers. All the remaining 67 patients had lung cancer, 58 of whom eventually received definitive treatment.

Patients with occult lung cancer are not a homogenous group. Consequently, reports from different institutions can and do vary, depending on the population from which the patient is derived.

If a patient with occult lung cancer is from the entire population at risk, that is, any patient who walks into my office and has a positive sputum cytology and a negative chest roentgenogram, this patient's cancer, when localized, may be of any cell type or stage. When eventually treated, this patient will have a survival consistent with these factors. On the other hand, if the patient is from a subgroup of patients who are in a sputum screening program, survival may be somewhat different. For example, if a patient in a sputum screening program is found to have a negative cytology initially, but with subsequent screening the cytology becomes positive, this patient has a high chance of having squamous cell carcinoma, frequently in situ, which, when localized and resected, will be a Stage I neoplasm having a very high survival rate.

In our series of 58 treated patients with occult lung cancer, 46 were from the general population and 12 were from our special screening program. All 12 patients in the latter group initially had negative sputum cytology. When the cancer was localized, 11 of the 12 patients had squamous cell carcinoma, 6 of which were in situ. The resectability rate in both groups was essentially the same, approximately 91%. However, when examined by stage, 83% of the patients in the general population had Stage I disease and 15% had Stage III. Of those patients in the screening program, however, 92% had Stage 0 or I disease and none had Stage III.

The incidence of associated cancers is also variable depending on how the data are presented. In our total group of 67 patients with occult lung cancer, 22 patients, or 33%, had another visceral cancer either before or after the occult lung cancer. However, only 19 patients, or 28%, had an associated lung cancer either before or after the occult lung cancer. On the other hand, of the 45 patients with no previous history of cancer in whom an occult lung cancer developed, only 5 patients or 11%, had a second lung cancer.

In our group of 58 treated patients followed for a mean of 40 months, 18 patients, or 31%, are dead. Seven patients died of lung cancer and the remainder mostly of coronary artery disease. Forty patients are alive, 36, or 90%, of whom have no evidence of disease.

I have several questions for Dr. Martini. He alluded to a 30% incidence of associated upper airway cancer. I wonder if in his personal experience it is that high. Second, were any of the cancers in his patients detected in a special screening program, and, if so, did they behave differently? Finally, does he think that occult lung cancer is a heterogenous group? Should we attempt to better stratify these patients?

DR. D. D. MUNRO (Montreal, Que, Canada): Twenty-one years ago, in June, 1959, *Newsweek* magazine featured New York's Memorial Cancer Center on its cover. I quote from the report: "Pending a major breakthrough in cancer research, the doctors look to earlier diagnosis Surgery alone can do no more." Now, 21 years later, we are just beginning to grapple with the problem.

I firmly believe the only way to gain some measure of control over this fatal disease is through early detection—match the history, control rate, and cure rate of cervical cancer. Dysplasia, in situ, and early invasive carcinoma of the lung are becoming an increasingly important component in at least partial control of this cancer. The mounting frequency with which the diagnoses are being made in different centers is directly related to several factors:

1. The experience, skill, and utilization of a bronchopulmonary cytopathologist. The landmark paper on this technique—that of Saccomanno and associates [1]—is well known.
2. The advances in technology and newer techniques in bronchoscopic localization of occult or in situ carcinoma.
3. The epidemic proportions of the problem and the screening of high-risk populations, particularly those with some transient sign or symptom.
4. The skill, enthusiasm, and interest of certain centers or groups in perfecting early detection techniques.

We at the Montreal Chest Hospital of McGill University have been interested in this problem for the last 10 years. At the moment we have a series of approximately 17 patients in whom the cancer was diagnosed, localized, and resected. Most cancers are found by what we term "programmed interval bronchoscopy." This means that patients with a consistent positive cytology and normal roentgenograms are placed on a routine of programmed interval bronchoscopy every 3 to 4 months until the cancer is found. In the past 20 months, we have identified and localized 12 patients with occult cancer. We now have on stream approximately 20 patients. Bronchoscopy will be continued at specific intervals as long as the sputum remains consistently positive, until we find the carcinoma. We think this approach is practical. Theoretically, the end results should be the same, provided the carcinoma is found when it is in the in situ stage.

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DR. F. G. PEARSON (Toronto, Ont, Canada): To those of you who were here at the Postgraduate Session, I apologize for presenting the same information, but it is, I think, particularly pertinent to the paper that Dr. Martini has given.

During a period of almost 20 years at Toronto General Hospital, we have accumulated 27 patients with radiologically occult tumors. The majority simply walk into the hospital, as Dr. Pairolero described. In only 3 patients were the tumors picked up in a small screening program. Many of these patients were seen initially with symptoms suggestive of or consistent with an early cancer, most had hemoptysis, and a small number had segmental pneumonia, which was sometimes transient and which cleared completely with antibiotic therapy.

The cell type again confirms the observations of Dr. Martini and his group. All but 2 were squamous cell carcinomas. Twenty-two, however, were invasive, 5 in situ. I think it of great note in this series that there were no nodal metastases in any surgical patient. Indeed, in 18 of the 21 patients, if the location had not been positively identified, there would have been no way of identifying the tumor by vision or palpation at the time of operation.

Twenty-one patients were managed by resection. Five were treated with radiotherapy. We were very disappointed with the results of radiotherapy in what should be the earliest and most curable stage of squamous cell cancer. Two of the patients died of recurrent cancer within 40 months of treatment.

The group managed by resection has been followed for almost 9 years on average. Only 1 patient has been lost to follow-up. None have died of the original primary. As in Dr. Martini's series, none are alive with local recurrence. I can't explain the absence of second primaries in this group. It may relate to the effectiveness of efforts to stop that population from smoking cigarettes.

I support what Dr. Pairolero said about occult cancers from different subgroups having a different biological behavior. In a group of patients with industrially related cancers at the International Nickel Company in Subry, 12 seen within the last 5 or 6 years with truly occult lesions underwent resection. Of these, 2 have second primaries already. One patient had nodal metastases at the time of operation and 1 has died of cancer. It looks as though this is indeed a different disease.

I have one question for Dr. Martini. In your patients with advanced disease, both squamous cell carcinoma and adenocarcinoma, I find it hard to imagine a Stage III lesion that is not big enough to be palpable and actually visible on chest roentgenogram. In these patients are the lesions hidden behind the heart or in some corner?

DR. MARTINI: I think there is very little difference in the discussants' presentations of their views on occult carcinomas of the lung. In specific reference to Dr. Pairolero, 15 patients in the study presented came from the screening program. There were also 8 head and neck carcinomas detected by sputum cytology from the same screening program. So, one-third of the roentgenographically occult cancers were of head and neck origin.

We have not observed any recurrence after resection for periods of follow-up from 1949 to the present, and this observation is also supported by Dr. Pearson's experience. Unlike Dr. Pairolero's observation, we have had 2 patients with occult carcinomas from the screening program who were found to have Stage III disease at thoracotomy. This may explain why radiotherapy without surgical staging has been disappointing in the treatment of these cancers.

I concur with Dr. Munro that it is unfortunate that sputum cytology and chest roentgenogram remain our only methods for lung cancer detection and that as yet there are no tumor markers for early detection.

Aggressive Surgical Management of Testicular Carcinoma Metastatic to Lungs and Mediastinum

Isadore Mandelbaum, M.D., Stephen D. Williams, M.D.,
and Lawrence H. Einhorn, M.D.

ABSTRACT **During the past six years, more than 200 patients were treated with chemotherapy for disseminated testicular cancer with a 70% complete remission rate. In 22 patients who were 17 to 46 years old, there was persistent thoracic disease, which was treated surgically. Six required a median sternotomy for bilateral pulmonary involvement or mediastinal metastasis.**

In 8 patients, chemotherapy had altered the histological appearance of the metastases from that of an undifferentiated primary tumor to a mature cystic teratoma. Five patients had nodules in the lungs, which were necrotic and fibrosed with no evidence of tumor. Nine showed embryonal cell carcinoma metastases in the lungs. All who had cystic teratoma are alive and free from disease. Three of the 5 with nodules and 1 of the 9 with metastases are currently free from disease.

Aggressive surgical intervention is important in this unique group of patients in order to determine the precise pathological category of the lesions, to remove intrathoracic malignancy, and to assess the need for additional chemotherapy. An operative mortality of zero and a low morbidity justify this approach.

Surgical management of metastatic pulmonary lesions from various primary sites have been reported previously and favorable prognostic factors defined [7, 8]. With improved chemotherapy and close cooperation between oncologist and thoracic surgeon, it has been possible to apply these principles and to formulate new ones in the treatment of metastatic testicular carcinoma of germ cell origin to the chest [1].

Testicular carcinoma is a disease of young men, and more than 200 patients with this type of disseminated cancer were treated at Indiana University Medical Center from 1974 through 1979. Twenty-one with metastases to the chest and 1 with metastasis to the supraclavicular area were selected for surgical treatment and constitute a unique and interesting subgroup.

The purpose of this paper is to present the results of combined thoracic surgical and chemotherapy treatment in these patients. Those with primary mediastinal carcinoma of germ cell origin are not included in this series.

Material and Methods

Since April, 1975, 22 patients with metastases to the chest or supraclavicular area from testicular carcinoma of germ cell origin were treated surgically. They ranged from 17 to 46 years old (mean, 26 years; median, 23 years). The primary tumor had arisen in the testis in 21 patients and as a primary retroperitoneal germ cell tumor in 1. Most patients had no pulmonary symptoms, but were seen with roentgenographic evidence of thoracic metastases. One patient had chest wall pain due to an extrapleural lesion with rib involvement, and 1 had hemoptysis due to pulmonary metastases.

The histological picture of the primary tumor was usually mixed and consisted of embryonal, teratocarcinomatous, and choriocarcinomatous elements. When initially seen, all patients had advanced disease and were classified in Stage III. All patients had had a radical orchiectomy, and 13 had had a previous retroperitoneal lymph node dissection before they were seen for chemotherapy.

Patients were evaluated by physical examination, posteroanterior and lateral chest roentgenograms, whole-lung tomograms, abdominal ultrasound and abdominal computerized axial

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tomograms (CAT scans), and determinations of serum beta subunit human chorionic gonadotropin (HCG) and α-fetoprotein levels. Selected patients had thoracic CAT scans.

All patients had received intensive courses of platinum, vinblastine, and bleomycin therapy following excision of the primary germ cell carcinoma. The exact chemotherapy schedule was detailed in a previous paper [1a]. Specific indications for thoracic procedures were limited to patients with (1) thoracic lesions and no other anatomical evidence of tumor, (2) thoracic lesions persisting after a full course of chemotherapy, (3) a solitary pulmonary lesion that had recurred after an initial chemotherapy-induced complete remission, and (4) good general health without any other systemic disease. The operation was performed one month or longer after the last chemotherapy treatment to allow full recovery from the toxicity of the chemotherapeutic agents.

Results

Since 1975, 21 patients with thoracic lesions and 1 with a supraclavicular lesion have been treated surgically. Five with bilateral lesions and a single patient with a solitary mediastinal lesion had a median sternotomy incision. Thirteen patients with a solitary lesion and 3 with multiple lesions limited to one lung were approached by a posterolateral thoracotomy or by excision of a supraclavicular mass (1 patient). The primary aim was to preserve as much normal pulmonary tissue as possible, and, therefore, most patients had wedge resection for each pulmonary lesion. As many as thirty lesions were removed in a single patient. In 3 patients, a lobectomy was carried out because of the central location of the lesion. In 1, pneumonectomy was performed because of hilar involvement. There was no operative mortality and minimal morbidity.

Fourteen patients had solitary lesions. Five were in the right lung, one in the right lung with extension into the extrapleural space and ribs, six in the left lung, one in the mediastinum, and one in the left supraclavicular area. Of these 14 patients, 6 had mature teratoma, 6 had embryonal carcinoma, and 2 had a necrotic, fibrotic area without evidence of tumor.

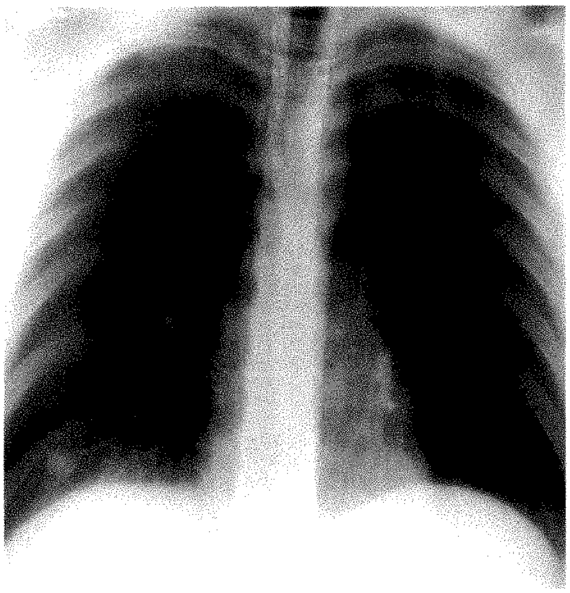

Fig 1. Solitary mass in the right lower lobe proved to be a mature teratoma.

Eight patients had multiple lesions. Three had involvement of one lung and 5 had bilateral involvement. The lesions consisted of embryonal carcinoma in 1 patient, three mature teratomas in 1, necrotic and fibrotic areas in 3 patients, a mature teratoma and an embryonal carcinoma in 1 patient, a mature teratoma and separate necrotic fibrotic tissue in 1, and embryonal carcinoma with separate fibrotic tissue in 1.

There was excellent correlation among CAT scans, whole-lung tomograms, and operative and histological findings. In only 1 patient was a lesion visualized with chest CAT scan not apparent on whole-lung tomography. In another patient, one lesion in the right lower lobe was diagnosed preoperatively, but an additional one each in the right lower and right middle lobes was found at operation. No preoperative roentgenographic study predicted accurately the type of histological lesion that was excised—teratoma, embryonal carcinoma, or fibrotic masses (Figs 1–3).

Four patients underwent thoracic resection within six months of resection of the primary testicular cancer. Three were operated on from between seven and twelve months; 8 from thirteen to twenty-four months, 6 from twenty-five to thirty-six months, and 1 was operated on eight years following testicular re-

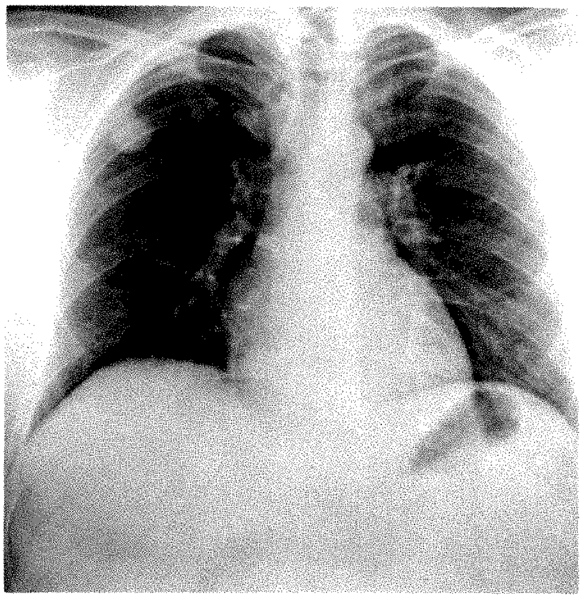

Fig 2. The solitary mass in the right upper lobe consisted of a discrete area of fibrosis and necrosis without any evidence of tumor.

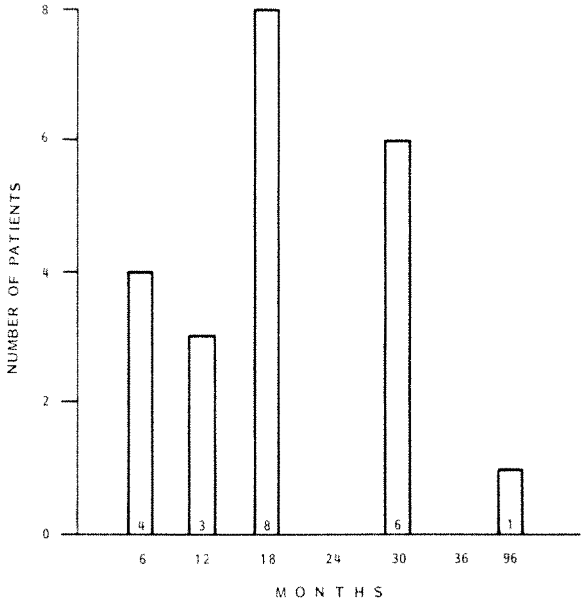

Fig 4. Fifteen patients (68%) were operated on for thoracic lesions within two years of resection of the primary testicular cancer.

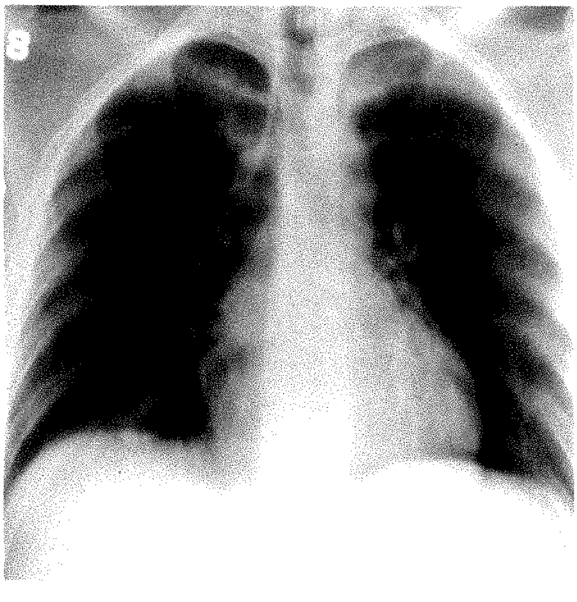

Fig 3. Solitary lesion in the right lower lobe proved to be metastatic embryonal carcinoma.

section. Of 8 patients with mature teratoma, 1 had thoracic resection three months after radical orchiectomy, 5 were resected thirteen to twenty-four months after removal of the primary lesion, and 2 from twenty-five to thirty-six months later (Fig 4).

At the present time, 12 patients are alive with no evidence of tumor from four months to two years following thoracic resection. Eight had had benign teratomas, 3 had had areas of fibrosis, and 1 had had a solitary embryonal carcinoma. Seven of 9 patients with embryonal carcinoma died. One is free from disease, and 1 had a cerebral metastasis, which was resected recently. Two of 5 patients who had areas of fibrosis without evidence of tumor died of cerebral metastases.

The HCG and α-fetoprotein serum levels were elevated prior to thoracic resection in 7 patients and were normal in 15. Four with elevated levels were discovered to have embryonal carcinoma, and 3 had discrete areas of fibrosis without evidence of tumor. However, in the latter 3 patients, embryonal carcinoma developed subsequently in the central nervous system in 2 and in the retroperitoneum in 1. Therefore, elevated HCG and α-fetoprotein serum levels correlated well with the finding of viable carcinoma in the chest or with the occult presence of embryonal carcinoma in other anatomical sites. The HCG and α-fetoprotein levels were normal in all patients with teratoma who had no other evidence of malignancy, in 2 patients with fibrotic areas, and in 5 with embryonal carcinoma of the chest. While abnormal preoperative serum levels of HCG and α-

fetoprotein correlated well with the presence of cancer, normal levels did not rule it out [5].

Comment

Many patients with thoracic metastases due to testicular cancer of germ cell origin have been treated effectively with chemotherapy without needing any operative intervention [1a, 6]. Our 22 patients were selected critically from more than 200 patients. After intensive chemotherapy, the criteria for thoracic surgery have been disease limited to the thorax or recurrence of disease, and no other major systemic disability.

The time interval between resection of the primary carcinoma and resection of pulmonary metastases as well as the number of metastatic nodules plays an important role in the prognosis of patients who have had carcinoma of the colon or uterus [7, 8], for example. These factors may not be as important in patients with thoracic metastases due to germ cell testicular cancer because of the results achieved with chemotherapy in these patients. Resection of multiple lesions in 8 patients resulted in 3 being alive free from disease for as long as twenty-one months, 2 are alive with disease, and 3 have died. Furthermore, thoracic resection was performed with excellent results in about 70% of our patients earlier than two years after removal of the primary testicular cancer.

Of greater prognostic importance in this series is the type of histological lesion found at the time of thoracic resection. If the lesion has been altered by chemotherapy so that a mature teratoma is present without any other malignant lesion [9], the patient has not died in this series. The finding of metastatic embryonal carcinoma in the chest, on the other hand, has been associated with death in 7 patients and recurrent cancer in 1. Only 1 of the 9 patients in this group is currently free from disease. In those patients with primarily fibrotic lesions, 3 are alive and free from disease, and 2 have recurrent embryonal cancer in the central nervous system. Retroperitoneal cancer developed in another patient, who underwent an additional operation, and is currently free from disease. These last 3 patients all demonstrated elevated HCG and α-fetoprotein serum levels.

It is evident from this unique group of patients that chemotherapy plays an important role in either eradicating all evidence of metastatic disease or in altering the histological characteristics of a substantial number of lesions from those of a wildly malignant tumor to either a mature teratoma or to an area of fibrosis and necrosis without evidence of viable carcinoma. Since there is no precise preoperative diagnostic technique differentiating among these three histological types, thoracic resection is important in order to remove every lesion and to obtain an exact diagnosis.

There has been considerable controversy concerning the finding of mature teratoma and the importance of this particular lesion [9]. Some regard it as a true malignant metastasis. Whether it is or not, since mature teratoma in other parts of the body has the potential to undergo malignant degeneration, we consider excision of this lesion mandatory. A late follow-up in our patients who have had mature teratoma resected without any evidence of malignancy indicates no other evidence of disease. Why all metastatic lesions from germ cell testicular cancer are not altered into mature teratoma remains an unanswered question. It is possible that some embryonal cancer metastases are resistant initially to chemotherapy or, more likely, that there is an initial response followed by cellular resistance. This latter explanation would seem to be more plausible in view of the fact that in most patients, as a result of chemotherapy, there is some regression of pulmonary metastases followed by recurrent embryonal cancer in some.

There have been reports of oxygen toxicity in patients who are operated on for thoracic metastases due to testicular cancer of germ cell origin [2]. Our patients were treated with the usual methods of respiratory support and with the usual concentrations of oxygen both during anesthesia and in the early postoperative period, without any evidence of pulmonary insufficiency. The reason for this discrepancy between our series and those reported in the literature remains speculative.

Rarely, germ cell cancers may arise primarily in the mediastinum and should be differentiated from metastatic lesions of testicular origin [3]. In our series, metastasis to the mediastinum secondary to a germ cell testicular cancer occurred in only 1 patient. Nevertheless, patients with mediastinal germ cell cancers must be screened carefully in order to rule out primary testicular carcinomas [4].

The psychological aspects are of extreme importance in the care of these young men. All have had alopecia due to chemotherapy, and all have had previous operation—radical orchiectomy and additional retroperitoneal node dissection in most. Many are married and are concerned about unknown factors such as the nature of the histological thoracic lesion, the possible disability following thoracotomy, the prognosis, and other personal problems. A team approach has helped us to understand these problems in each individual patient and to psychologically support the patient and family during the trying preoperative and postoperative periods.

At present, the cure rate for patients with disseminated testicular cancer is approaching 70%. The majority of patients with pulmonary metastasis do not require operation since they most frequently achieve complete remission with chemotherapy alone. It has been a source of personal gratification that in a disease that was almost universally fatal and is the most common cause of cancer in the young adult male, our combination of chemotherapy and surgical intervention in these selected patients has resulted in no operative mortality and minimal morbidity. Also, 12 of 22 patients (54%) currently are alive and disease-free.

After completing this study, we arrived at the following conclusions:

1. In a series of 22 patients with thoracic metastases due to germ cell carcinoma of testicular origin, complete excision of the thoracic lesions was carried out utilizing either a median sternotomy incision or in unilateral lesions, a posterolateral thoracotomy. Limited resections are desirable. In 1 patient, a supraclavicular mass was excised.
2. Before surgical intervention is considered, these patients should receive an intensive course of chemotherapy.
3. In patients with persistent thoracic lesions or with recurrent lesions, three types of histological pictures are observed—mature teratoma, fibrosis and necrosis without evidence of tumor, and embryonal cell carcinoma.
4. Preoperative roentgenographic diagnostic methods do not differentiate among these three histopathological forms.
5. In all patients with elevated serum HCG and α-fetoprotein levels, there was embryonal cell cancer in the chest or it subsequently developed in the abdomen or brain. The levels were normal in all patients with teratoma and in 5 patients with embryonal cancer of the chest.
6. In contradistinction to pulmonary metastases from nontesticular primaries, the presence of solitary or multiple lesions and the time interval between resection of the primary germ cell cancer of testicular origin and the pulmonary lesions have no bearing on the ultimate prognosis.
7. Aggressive surgical intervention is important in this unique group of patients in order to determine the precise pathological category of the lesions, to remove intrathoracic malignancy, and to assess the need for additional chemotherapy.
8. This approach is justified by three chief results: an operative mortality of zero, a low morbidity, and a cancer-free rate of 54%.

Addendum

Since submission of this paper, 10 additional patients have been operated on for testicular germ cell cancer metastatic to the chest. Five had a median sternotomy for bilateral lesions, and 2 had thoracotomy for unilateral ones. Three additional patients had a median sternotomy for bilateral disease performed at the same time of retroperitoneal dissection. Of these 10 patients, 3 had mature teratoma, 4 had areas of fibrosis and necrosis, and 3 had metastatic cancer. Postoperative morbidity was minimal, and again, no mortality was observed.

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Discussion

DR. EDWARD J. BEATTIE, JR. (New York, NY): I had the privilege of reading Dr. Mandelbaum's paper and enjoyed it very much. This report on metastatic germ cell tumors, of which the embryonal cell carcinomas primarily are the bad actors, is the most exciting study of cancer in adults to be presented in the past ten years. Dr. Mandelbaum's paper is very timely indeed.

Ten years ago I saw a patient who had embryonal cell carcinoma in the chest. He was dead in 6 months despite use of the best known therapy—three operations, internal radiotherapy, external radiotherapy, and chemotherapy. A Stage III embryonal cell carcinoma of the testicle with metastases to the abdomen, chest, and neck resulted in death before 12 months. So what you are hearing today is truly revolutionary.

I have shown survival curves supplied by Dr. Robert Golbey, Chief of Chemotherapy at Memorial Hospital, and obtained with our VAB Program. It began with VAB I. We are now up to VAB VIII, which contains seven drugs. You will see that VAB I resulted in a cure rate at five years of up to 30%. We now expect to cure almost 80% of patients with Stage III embryonal cell carcinomas. That is really spectacular.

The important thing stressed by Dr. Mandelbaum is that only 22, or 10%, of his patients had to have chest operation. This is because the chemotherapy was so good.

He demonstrated very well that the lesions cannot be identified properly until they are looked at under the microscope. An important concept today is "in vivo chemotherapy sensitivity testing." He demonstrated that when chemotherapy killed the cancers, the patients all survived unless there was cancer someplace other than in the chest.

Patients with metastases in the lungs who are alive and well 24 months later have, in our experience, all been cured. So, the 24-month period is critical.

One final point I think is important. In his paper, Dr. Mandelbaum mentioned respiratory failure following chest operation in patients who were on intensive chemotherapy. He had none in his series. However, there are some patients receiving intensive chemotherapy, particularly with high doses of bleomycin, who do go into respiratory failure following thoracotomy. The anesthetists at Memorial Hospital have demonstrated the cause to my satisfaction. They believe the cause is oxygen toxicity from the standard high-dose oxygen usually used during thoracotomy, especially if the patient is considered a bad risk. In our patients with lung cancer who have had chemotherapy, the oxygen concentration is kept to 24% or less during operation. No respiratory distress syndromes after operation have been seen in these patients.

Dr. Mandelbaum stated he used "usual oxygen." What is usual oxygen in Indiana?

DR. MANDELBAUM: I thank Dr. Beattie very much for his kind comments. He, of course, has led the field in the treatment of metastatic disease to the chest.

This unique group of patients was presented today because it represents an unusual type of response of malignancy to chemotherapy. Perhaps it illustrates what the future holds in terms of treatment of other metastatic disease and the possibility of combining operation with other therapeutic modalities. Dr. Beattie and his group have guided us all in this direction.

As for oxygen toxicity, I have been aware of this in the literature and am alert to the possibility of it occurring. However, I have not encountered this problem in the present series. I don't know the precise explanation. Perhaps at our center we operate on patients who have not had as much chemotherapy as those reported in other groups with oxygen toxicity. At Indiana University Medical Center, the usual oxygen concentrations in patients during the operative and early postoperative periods range from an $F_{I}O_2$ of 30 to 45%.

Stresses of Natural versus Prosthetic Aortic Valve Leaflets in Vivo

Mano Thubrikar, Ph.D., William C. Piepgrass, M.D.,
J. David Deck, Ph.D., and Stanton P. Nolan, M.D.

ABSTRACT **During normal function of the aortic valve, the aortic leaflets undergo not only cyclic loading and unloading but also cyclic reversal of their curvature. The stresses induced in the leaflet due to these variations have been computed using a new concept based on the structure of the leaflet. Membrane stresses have been related to the pressure difference across the leaflet and bending stresses to the leaflet curvature. Total stresses were obtained by adding the two stresses. Total stresses in bioprosthetic and synthetic leaflets also were computed using the same approach. In systole, the natural leaflet is subjected to much lower total stress than a bioprosthetic or a synthetic leaflet. The natural leaflet is not subjected to compressive stresses during the cardiac cycle, whereas bioprosthetic and synthetic leaflets must sustain compressive stresses during systole. The differences in stress patterns of these leaflets indicate that there is a difference in their longevity.**

As the natural aortic valve opens and closes, the valve leaflets undergo cyclic loading and unloading and cyclic reversal of their curvature in the circumferential direction. Loading and unloading is a result of high and low pressure gradients across the leaflet in diastole and in systole, respectively. The reversal of curvature is a result of change in the leaflet configuration from diastole to systole (Fig 1). Loading and unloading causes a change in length and causes leaflet fatigue, which could be minimized by increased stiffness of the leaflet. On the contrary, the reversal of curvature causes flexion stresses, and flexion failure could be minimized by decreased stiffness of the leaflet. Since the natural leaflet is subjected to both of these effects in the circumferential direction, it is only logical that the leaflet has a variable elastic modulus in the circumferential direction [12]. The leaflet has a higher elastic modulus (high stiffness) in diastole, which reduces changes in the leaflet length, and a lower elastic modulus (low stiffness) in systole, which reduces flexion stresses [12]. It is important to know the type and magnitude of the stresses that develop in the leaflet as a result of these two phenomena, in order to understand how the natural leaflets withstand these stresses during billions of cardiac cycles.

Although the natural leaflet has principal stresses in both the circumferential and the radial directions, only the stresses in the circumferential direction were analyzed in this study because the leaflet is subjected to the phenomena just mentioned only in the circumferential direction. Also, they represent the stresses in the body of the leaflet and do not include the zone of leaflet attachment.

In this study, a simple, new approach is presented to the computation of stresses in the circumferential direction of the leaflet during normal function of the natural aortic valve in vivo. The approach is extended further to determine similar stresses in bioprosthetic and synthetic leaflets. In order to determine stresses in the leaflet in vivo, the following information is required: (1) the structure of the natural aortic leaflet; (2) the stress-strain curve of the natural aortic leaflet in vivo and in vitro; (3) the stress-strain curve of porcine leaflets fixed in 2% glutaraldehyde; and (4) the stress-strain curve of Avcothane, a synthetic that has been used as leaflet material in some experimental protheses.

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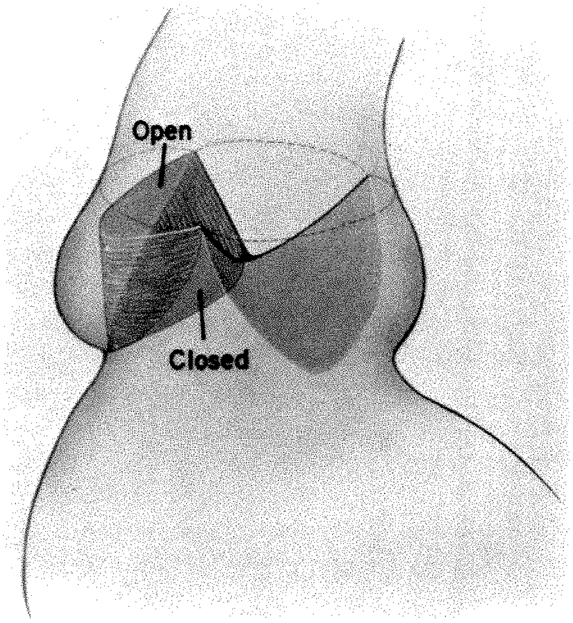

Fig 1. A natural aortic valve showing one leaflet in the open and closed position. For this leaflet, the aortic surface (shown by parallel dotted lines) forms the outer curve in the open position and the inner curve in the closed position, indicating complete reversal of the leaflet curvature. The second leaflet is drawn in the closed position.

Theory and Methods

The structure of the aortic valve leaflets was studied using canine aortic roots fixed for histology in the closed position with glutaraldehyde at 80 mm Hg pressure and serially sectioned. Methacrylate sections cut at 1 μ were stained with azure to show the distribution of connective tissue fibers and semifluid ground substance. The ground substance contains complex saccharidic molecules. The presence of these molecules causes a metachromatic shift of the azure staining, thereby indicating the location and concentration of the ground substance within the leaflet.

The stress-strain curves of natural aortic leaflets were determined in the circumferential direction of the leaflets in vivo and in vitro for dogs in our previous study [12]. Six porcine aortic leaflets were fixed in 2% glutaraldehyde (bioprosthetic leaflets). From each leaflet, a rectangular strip (approximately 12 mm long and 3 mm wide) was cut in the circumferential direction of the leaflet (Fig 2). For each of these strips, the stress-strain curves were determined, in vitro, using an Instron tensile-testing machine (strain rate 5 mm per minute). The stress-strain curve for Avcothane was obtained from published data [5].

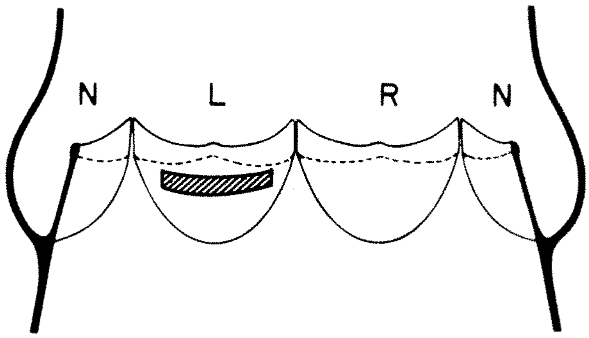

Fig 2. An aortic valve. L, R, and N are the leaflets corresponding to the left, right, and noncoronary sinuses, respectively. A rectangular strip cut from the leaflet in the circumferential direction for stress-strain studies is indicated.

The stresses in the circumferential direction were calculated as follows: An externally applied load such as pressure induces internal force (or stress) in the leaflet and also produces stretching (or strain) of the leaflet. In vivo, the load (pressure) on the leaflet varies from systole to diastole, thereby changing the stresses in the leaflet from systole to diastole and also changing the leaflet length from systole to diastole. In vivo, the load on the leaflet varies cyclically in such a way that it produces a change in the leaflet curvature in the circumferential direction from systole to diastole. This change in the leaflet curvature produces additional stresses in the leaflet.

Consider for a moment that the change in the leaflet curvature occurs by bending. Then, to calculate the stresses in the leaflet in the circumferential direction, both the stretching—the change in the leaflet length from systole to diastole—and the bending that occurs as a result of change in the leaflet curvature should be considered simultaneously. However, for the large strains that occur in the leaflet, there is no standard procedure for the calculation of stresses that considers stretching and bending simultaneously. In the present work, therefore, stretching and bending are considered independently and separately for the systolic and diastolic phases. This consideration not only simplifies the procedure for stress calculation, which would otherwise be tedious and time-consuming, but also yields stress values that are good approximations.

The stress due to stretching of the leaflet, calculated by neglecting bending, is called membrane stress. Membrane stress is tensile in the leaflet (as will be seen later) throughout its complete thickness. The stress due to bending of the leaflet, calculated by assuming that the configuration of the leaflet in systole and diastole is achieved by bending alone, is called bending stress. Bending stress is tensile in the half of the thickness of the leaflet on the convex side and compressive in the half of the thickness of the leaflet on the concave side. Total stress in the leaflet in the circumferential direction is obtained by adding membrane stress and bending stress, with due consideration to their tensile or compressive nature.

In all the leaflets, membrane stress in the circumferential direction was calculated using the cylindrical geometry of the leaflet and the equilibrium equation [6]. Membrane stress = PR/T, where P is pressure difference across the leaflet, R is radius of the leaflet, and T is thickness of the leaflet. For the natural aortic leaflet, membrane stress is calculated using P = 80 mm Hg in diastole and 5 mm Hg in systole; R = 9 mm in diastole and 10 mm in systole; and T = 0.4 mm. The pressure difference across the leaflet in diastole was measured in vivo, and was in the range of 60 to 100 mm Hg [12]. Driscol and Eckstein [4] measured a pressure difference of 9.4 mm Hg across the leaflet during early systole, in vivo, and found that the gradient decreased during systole. The radius of the leaflet in diastole and in systole also was measured [12] in vivo considering that the leaflet is cylindrical, as has been observed by us [10, 11] and others [9]. The thickness of the leaflet also was measured.

Membrane stresses in bioprosthetic leaflets and in Avcothane leaflets were calculated using P, R, and T values of the natural aortic leaflet. This assumes that valves made with bioprosthetic leaflets or with Avcothane leaflets would open and close in the same manner as the natural valve. Membrane stresses in diastole and in systole calculated on this assumption are the same for all types of leaflets. Also, the membrane stresses are tensile in both diastole and systole because the pressure inside the cylinder is greater than that outside the cylinder. The reason for this is that in diastole, the pressure on the aortic side of the leaflet, which at that time is the inside of a cylinder, is greater than that on the ventricular side of the leaflet. In systole, the pressure on the ventricular side of the leaflet, which at that time is the inside of a cylinder, is greater than the pressure in the aortic sinus. These stresses are plotted on the stress-strain curves of all the leaflets.

During normal function of the natural aortic valve, the change in leaflet curvature in the circumferential direction must be achieved by the processes of bending, shearing, or buckling. The histological structure of the natural leaflet suggests that the change is achieved by a combination of bending and shearing processes. However, due to the inhomogeneity of the leaflet, shear stresses are difficult to calculate. In the present work, therefore, only the bending stresses are calculated. The leaflet structure resembles an assembly of cables (collagen cords) running in parallel in the circumferential direction. Thus, the bending strain in the leaflet (i.e., in the cable) in the circumferential direction = T/2R [7]. The neutral shape of the leaflet was assumed to be flat (Fig 3). This assumption can be justified three ways: (1) it results in minimum bending stress in the leaflet, which is in favor of leaflet longevity; (2) in the excised heart, the natural aortic valve remains open when the pressures on both sides of the valve equilibrate; and (3) in vivo in the functioning valve, the leaflets were observed to remain in the open position when the ventricular pressure was equal to the aortic pressure [10]. The structure also suggests that the collagen cords or cables are free to bend in the circumferential direction without any major resistance from the fibers running in another direction. Thus, Poisson's effect can be neglected and bending stress can be found from the equation E × (T/2R), where E is the modulus of elasticity.

For bioprosthetic leaflets and Avcothane leaflets, the change in curvature in the circumferential direction is achieved by bending; any other mechanism would require greater

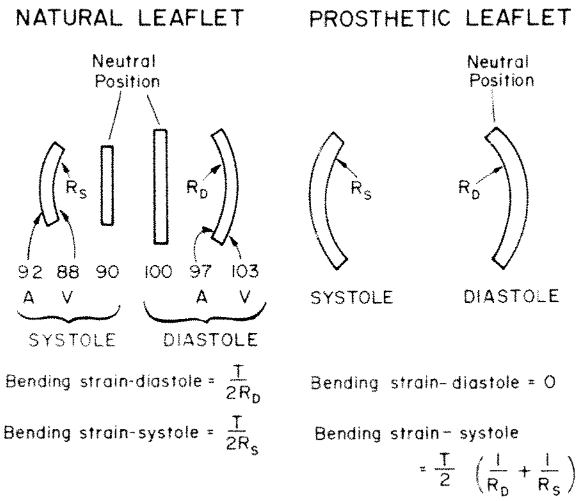
NATURAL LEAFLET
PROSTHETIC LEAFLET
Neutral Position
Neutral Position
R_S
R_D
R_S
R_D
92 88 90
100 97 103
A V
A V
SYSTOLE
DIASTOLE
SYSTOLE
DIASTOLE
Bending strain-diastole = $\frac{T}{2R_D}$
Bending strain-systole = $\frac{T}{2R_S}$
Bending strain- diastole = 0
Bending strain- systole $= \frac{T}{2}\left(\frac{1}{R_D} + \frac{1}{R_S}\right)$

Fig 3. Configurations of natural and prosthetic leaflets. If the natural leaflet is 90 mm long in systole and 100 mm long in diastole and if the leaflet changes configuration by bending, then the length of the ventricular (V) *side of the leaflet would change from 88 mm to 103 mm (or ≈ 15%), and the length of the aortic* (A) *side of the leaflet would change from 92 mm to 97 mm (or ≈ 5%).* (R = *radius of leaflet);* s = *systole;* D = *diastole;* T = *thickness of leaflet.)*

stress. Also, the bending strain in the circumferential direction = T/2R if the neutral position of the leaflet is flat. However, the neutral shape of bioprosthetic leaflets is curved in diastole since bioprosthetic valves are prepared by fixation of the natural porcine valve in the diastolic position. Similarly, the neutral shape of Avcothane leaflets is considered to be curved in diastole since Avcothane prosthetic valves are usually designed in the diastolic position. In both cases, the bending strain in diastole would be zero and the bending strain in systole would be (T/2Rd) + (T/2Rs), where Rd and Rs are radii in diastole and systole, respectively (see Fig 3). These leaflets behave like a plate, rather than an assembly of cables, and there is resistance from the radial direction to bending in the circumferential direction because the fixation process increases the stiffness of the leaflet in both directions. Thus, taking into account Poisson's effect, bending stress =

$$[E/(1 - \mu^2)]\,[(T/2Rd) + (T/2Rs)]$$

where μ is the Poisson ratio.

The bending strain for a leaflet calculated in the manner just described is the maximum strain. Bending stress for a leaflet could theoretically be calculated from these equations only if E (modulus of elasticity) is constant. The stress-strain curves of the natural and bioprosthetic leaflets indicate, however, that E is changing with the strain. Therefore, the bending stress was obtained by plotting the bending strain on the stress-strain curve and then reading the stress value.

The bending strain is plotted as follows: The natural leaflet, in diastole, has a membrane stress that is tensile and constant throughout the thickness of the leaflet. In addition, the leaflet is curved and has a compressive bending strain in half of its thickness and a tensile bending strain in the other half. The resulting bending stress is additive to the membrane stress in half the thickness of the leaflet because both the stresses are tensile, and it is subtractive in the other half because one is compressive and the other is tensile. Therefore, the bending strain is plotted on both sides of the membrane stress, and the result is a distribution of total stress throughout the thickness of the leaflet. To obtain the total stress in the natural leaflet in systole, a similar procedure is followed.

For bioprosthetic and Avcothane leaflets, membrane stress represents total stress in diastole since there is no bending strain. In systole, the distribution of total stress throughout the thickness of these leaflets is obtained by plotting the bending strain on both sides of the membrane stress as described already. Total stress = membrane stress ± bending stress, as in the two equations that follow.

Total stress in the natural leaflet in diastole or in systole = $(PR/T) \pm E \times (T/2R)$ (1)

Total stress in the prosthetic leaflet in systole = $(PR/T) \pm [E/(1 - \mu^2)]\,[(T/2Rd) + (T/2Rs)]$ (2)

Results

When the natural leaflet of the aortic valve is seen with the unaided eye from the aortic aspect, it appears to consist of a series of cords or cables suspended from an aortic wall parallel to the free edge of the leaflet. Histological inspection of the leaflet readily shows the cords as ripples or bulges on the aortic surface (Fig 4).

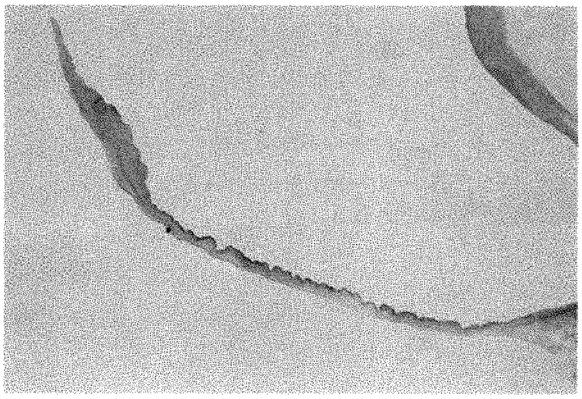

Fig 4. Vertical section of an aortic valve leaflet. The aortic surface of the leaflet is corrugated and densely stained due to ridges of dense collagenous tissue. Ridges represent the transverse sections of generally parallel tendinous cords. The cords are interconnected by thinner sheets of fibrous tissue. (Methylene blue–azure; magnification ×9.)

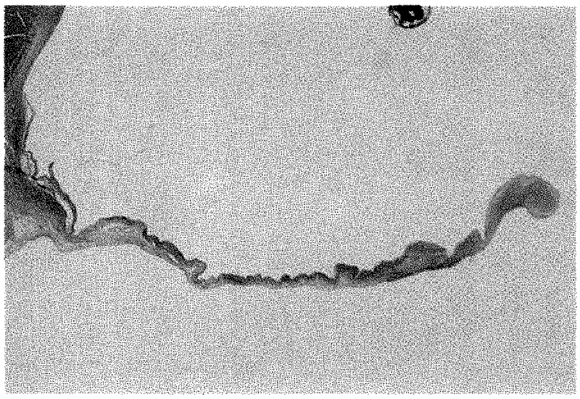

Fig 5. Similar vertical section of valve leaflet. Dark blue stain indicates dense tissue immediately beneath the aortic surface. Looser, more stringy tissue of leaflet core appears to the left. Faint tinges of purple within both core and dense tissue represent location of complex sugars (glycosaminoglycans) within connective tissue ground substance. (Methylene blue–azure; magnification ×9.)

The cords are composed principally of collagenous fibers and matrix materials. Toward the free edge of the leaflet, the space between the cords is occupied by much thinner sheets of similarly oriented collagenous fibers; toward the base of the leaflet, fibers in the cords and sheets cross each other more frequently and provide a partially woven structure. Just beneath the ventricular endothelium runs a very thin sheet of mostly radial collagenous and elastic fibers. Between this sheet and the cordal structure, the bulk of the tissue is a jellylike, watery ground substance or matrix material, in which scattered, radially directed collagenous and elastic fibers are embedded. Besides water, the principal molecular constituents of this ground substance are complex polysaccharides (glycosaminoglycans). These materials are metachromatic in azure-stained histological sections, and their concentration and distribution can be inferred from the intensity of purple staining in such sections (Fig 5).

Since the thickness and density of collagenous cords are several times greater than other fibrous areas of the leaflet, the cords have the principal role in its mechanical properties. In most places, the collagenous cords are free to bend in the circumferential direction without major resistance from fibers running in another direction. Whenever the matrix material is present, whether in the body of the leaflet or within the cords, its substance can move fairly easily, thereby allowing a relative movement (shear) between tissue elements surrounded by it. An electron micrograph of one of the collagen cords at the aortic surface of the leaflet (Fig 6) shows the fibers in it to be composed of tiny, round collagenous microfibrils, spaced apart evenly by a filamentous matrix material. Special cytological stains can show that the filamentous matrix material belongs to the family of glycosaminoglycans found more abundantly in the watery ground substance within the leaflet. This suggests that the shear so evident in this watery core can also occur within and between the collagenous cords.

The typical stress-strain curves of the natural canine leaflet, the bioprosthetic leaflet, and the Avcothane leaflet are shown in Figure 7. All of the curves were determined in the circumferential direction of the leaflets. The difference between these three curves is apparent in the low modulus region, which is present for a large extension of the natural canine leaflet and a small extension of the bioprosthetic leaflet, and is absent for the Avcothane leaflet. The membrane stresses in the circumferential direction (PR/T) are 1.7 gm/mm^2 in systole and 24.5 gm/mm^2 in diastole for all the leaflets and are shown in Figure 7 also. The values used for calculation of membrane stresses for all the leaflets are as follows: in systole, P = 5 mm Hg;

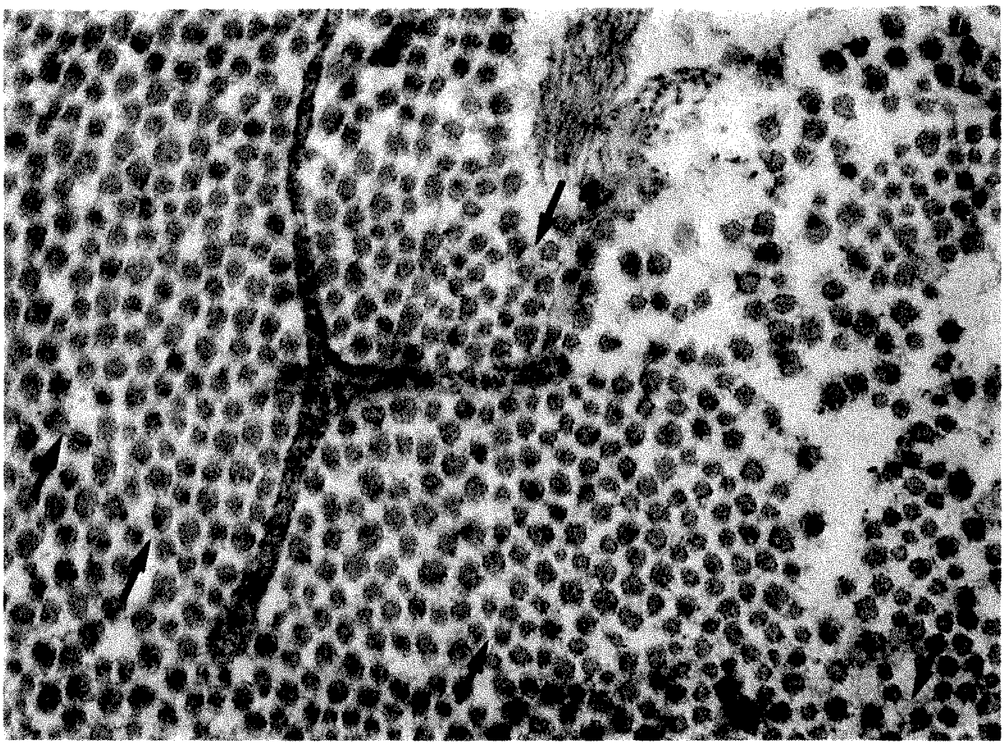

Fig 6. Electron micrograph through collagenous cords at the aortic surface of the leaflet. Collagenous fibrils make up the cord and cluster around a Y-shaped cellular process. Filamentous connections between the cross-sectioned fibrils represent glycosaminoglycans (arrows). *(Magnification ×48,000.)*

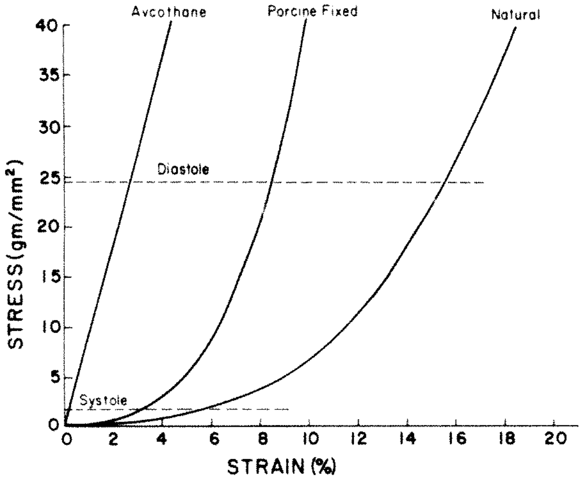

Fig 7. Stress-strain curves of the natural canine aortic, the porcine fixed (bioprosthetic), and the Avocothane leaflets. The dotted lines represent membrane stresses for all the leaflets.

R = 10 mm; and T = 0.4 mm; and in diastole, P = 80 mm Hg; R = 9 mm; and T = 0.4 mm. The membrane stresses are tensile in all the leaflets.

Bending strain (T/2R) in the circumferential direction for the natural leaflet is 2% in systole and 2.2% in diastole (Table). For both the bioprosthetic and Avcothane leaflets, the bending strains in systole [(T/2Rd) + (T/2Rs)] are 4.2% and in diastole, zero. The bending strains are tensile in half the thickness of the leaflet on the convex side and compressive in the other half on the concave side. For all the leaflets, the bending strains are superimposed on both sides of the membrane stress in order to obtain the total stress in the circumferential direction.

Figures 8, 9, and 10 show the superimposition of the bending strains and the membrane stresses on the stress-strain curve. In diastole, the natural leaflet has a large bending stress (see Fig 8). The bending stress is tensile on the ventricular side (convex side) of the leaflet and, therefore, is additive to the membrane stress. The bending stress is compressive on the aortic side (concave side) of the leaflet and, therefore, is subtractive to the membrane stress. The resulting total stress is variable throughout the thickness of the leaflet. It is

Stresses in the Natural Aortic, Bioprosthetic, and Avcothane Leaflets

	Bending Strain (%)		Total Stress after Bending (gm/mm²)[a,b]			
			Systole		Diastole	
Leaflet	Systole	Diastole	Aortic Surface	Ventricular Surface	Aortic Surface	Ventricular Surface
Natural	2	2.2	9.0	0.3	9.2	75
			5.5	0.6	9	52
			4	0.5	11	51
			3.5	0.75	15	36.2
Bioprosthetic	4.2	0	29.3	−2.4	24.5	24.5
			28.0	−1.3	24.5	24.5
			22.7	−0.7	24.5	24.5
			13.3	−0.5	24.5	24.5
			10.7	−0.7	24.5	24.5
			9.3	−0.5	24.5	24.5
Avcothane	4.2	0	53.3	−48.7	24.5	24.5

[a] Each value of the total stress is obtained from a single stress-strain curve. In these calculations, the Poisson ratio $\mu = 0.5$.

[b] A minus sign indicates compressive stresses; no sign indicates tensile stresses.

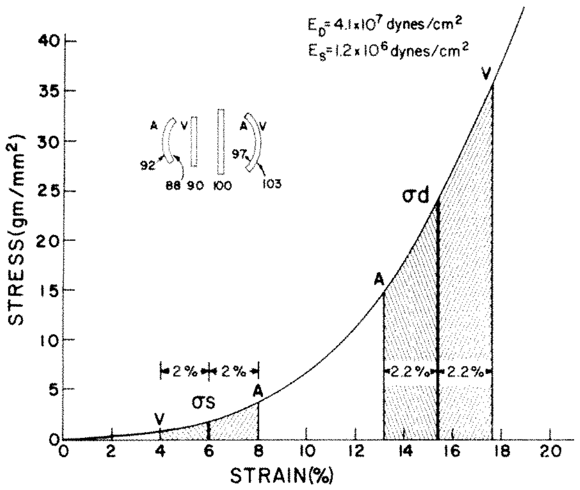

Fig 8. Stress distribution in the natural aortic leaflet. The σd and σs are membrane stresses in diastole (D) *and systole* (S)*, respectively. In diastole, the bending strain of 2.2% is drawn on both sides of σd. In systole, the bending strain of 2% is drawn on both sides of σs. The change in the stress and strain during a cardiac cycle is more for the ventricular* (V) *surface than for the aortic* (A) *surface. The shaded area represents the amount of bending energy stored in the leaflet.* (E = *modulus of elasticity.*)

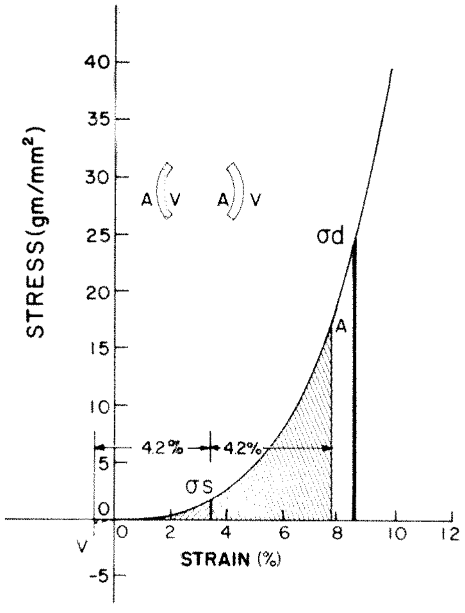

Fig 9. Stress distribution in the porcine leaflet. The mirror image of the curve is drawn in the compressive stress (negative) region. In diastole, the membrane stress σd also represents total stress. In systole, the bending strain of 4.2% is drawn on both sides of σs to obtain the distribution of total stress. (A = *aortic;* V = *ventricular.*)

minimal on the aortic surface and maximal on the ventricular surface. In systole, the natural leaflet has a small bending stress. Unlike diastole, in systole the bending stress is compressive on the ventricular side (concave side) and tensile on the aortic side (convex side). The resulting total stress is minimal on the ventricular surface and maximal on the aortic surface. The Table shows the magnitude of total stress on the aortic and ventricular surfaces in systole and diastole of four natural leaflets. The stress on the aortic surface is 4 to 9 gm/mm² in systole

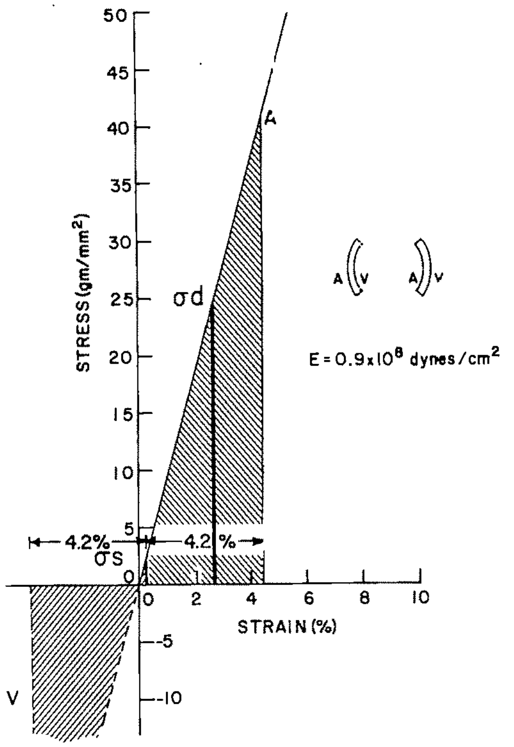

Fig 10. Stress distribution in the Avcothane leaflet. In diastole, the membrane stress σd also represents total stress. In systole, the bending stress of 4.2% is drawn on both sides of σs to obtain the distribution of total stress. (A = *aortic;* V = *ventricular;* E = *modulus of elasticity.)*

and 9 to 15 gm/mm² in diastole. The stress on the ventricular surface is 0.3 to 0.8 gm/mm² in systole and 36 to 75 gm/mm² in diastole. It is important to note that the total stress is tensile throughout the thickness of the leaflet at all times in a cardiac cycle.

In diastole, the bioprosthetic leaflet and the Avcothane leaflet have no bending stress because they are prepared in the diastolic position (see Figs 9, 10). The total stress in these leaflets is the same as the membrane stress in diastole (24.5 gm/mm²), and it is distributed evenly throughout the thickness of the leaflets. In systole, both the leaflets have large bending stresses. Once again, the bending stresses are compressive on the ventricular side and tensile on the aortic side. The total stress is variable throughout the thickness of both types of leaflets. It is minimal on the ventricular surface and maximal on the aortic surface. The Table shows the magnitudes of total stress on the aortic and ventricular surfaces in systole of six bioprosthetic leaflets and one Avcothane leaflet. The total stress was obtained when the stress value measured directly from the stress-strain curve was multiplied by a factor $[1/(1 - \mu^2)]$ to allow for Poisson's effect. In systole in the bioprosthetic leaflets, the stress on the aortic surface is 9.3 to 29.3 gm/mm² and on the ventricular surface, −0.5 to −2.4 gm/mm². In the Avcothane leaflet, the stress on the aortic surface is 53.3 gm/mm² and on the ventricular surface, −48.7 gm/mm². Higher bending stresses in these leaflets are due to the fact that the low modulus region is either absent or is present only for small strains and due to their higher bending strains. More important, the total stress is compressive on the ventricular surface in both types of leaflets in each cardiac cycle during systole.

Comment

Cataloglu and associates [2] calculated the stresses in aortic valve leaflets in diastole using silicone rubber casts of the aortic valve and the method of finite element analysis. Chong and co-workers [3] did the same calculations using the membrane theory. Swanson and colleagues [8] calculated bending stresses in the leaflet in the radial direction during the process of valve opening. Though these studies produced preliminary information on the stresses, they did not analyze cyclic configurational changes that occur in the leaflet in vivo. The limitation of their results is due to the in vitro observations of aortic root casts rather than in vivo observations of leaflet geometry.

This study presents a simple, new approach to the computation of stresses in the natural aortic leaflet throughout the cardiac cycle, based on in vivo observations of leaflet geometry. It considers the structure of the leaflet and, based on that structure, proposes that bending stresses are associated with the changing leaflet curvature and that membrane stresses are associated with changing leaflet length from systole to diastole. It gives a physical picture of the behavior of the leaflet in vivo and yields stress values that are good approximations. It also considers the stress-strain curve of functional importance in vivo.

Stress-strain curves of the natural leaflet show that the leaflet has an initial systolic "elastic phase" of low modulus followed by a diastolic "inelastic phase" of high modulus (see

Fig 7). The membrane stress is low in systole and high in diastole. This means that the leaflet must change length from systole to diastole, which has been observed in a previous study [12]. That study also established that, in vivo, the leaflet has a low modulus of elasticity in systole and a high modulus of elasticity in diastole.

Bending is the most likely mechanism for the reversal of leaflet curvature in vivo. If this, in fact, is true, then from Figures 3 and 8 it can be seen that the change in the length of the ventricular surface is much greater than the change in the length of the aortic surface of the leaflet as the leaflet moves from systole to diastole. This was observed to be the case in our previous study [12]. However, this is only suggestive (not conclusive) that the process of bending is the mechanism for change in leaflet configuration, since the differences in length changes could be explained another way. The radiopaque markers used to measure leaflet length in vivo were 1 to 1.5 mm in diameter. Although the markers were placed against the leaflet, their centers lay slightly away from the leaflet surface. The difference between the actual surface of the leaflet and the imaginary surface indicated by the markers could also explain the observation just mentioned [12].

Another possible mechanism for reversal of leaflet curvature is shear deformation within the leaflet. In a homogeneous material, shear deformation requires much greater stress than does bending deformation. Because the natural leaflet is nonhomogeneous and has a jellylike substance that can move with little force, shear is possible within the leaflet. Thus, the natural leaflet may undergo both bending and shear, and the actual stress in this case would be less than the calculated stress.

In calculating the bending strain in diastole and systole, the thickness of the leaflet was assumed to be constant. Actually, the thickness of the leaflet decreases from systole to diastole as the length of the leaflet increases. This would decrease the bending stress even more in diastole. In calculating the stresses, Poisson's effect was neglected. This is perhaps acceptable for the bulk of the leaflet, as suggested by its structure. However, it may be more appropriate to consider Poisson's effect for the stresses in the basal region of the leaflet because the collagen fibers here appear to cross each other more frequently. This would increase the stresses by as much as 25% depending on Poisson's ratio. This increase in the stress, however, is not likely to damage the leaflet since the leaflet is able to sustain the higher stress imposed by increased blood pressure. It is, rather, the compressive stress that is damaging to the leaflet [1]. The present study suggests that compressive stresses do not occur in the body of the leaflet during the cardiac cycle. It is concluded that the natural leaflet maintains its longevity, at least in part, through the absence of compressive stress and through low total stresses (relaxation) during systole.

In calculating the stresses in bioprosthetic and Avcothane leaflets, it is assumed that these leaflets are designed (except for their neutral position) and function the same as the natural leaflet. We do not believe that the valves made of bioprosthetic leaflets and of Avcothane leaflets open in the same manner as the natural aortic valve. However, the purpose of this assumption is to show that, based only on the intrinsic property (stiffness) of various leaflets, the stresses induced in those leaflets would be different. Conversely, the different stresses in these leaflets should suggest that they will not open in the same manner as natural leaflets.

Bioprosthetic and Avcothane leaflets have high bending stresses and high stored bending energy in systole (see Figs 9, 10). High stored energy would tend to push the leaflet towards the axis of flow, and therefore an increased pressure gradient across the leaflet would be required in systole to maintain the leaflets in the open position. In the absence of a high pressure difference across the leaflet, the valve would tend to close, thereby reducing the size of its orifice. In prosthetic leaflets, the increased stiffness and original formation in the diastolic position cause increased total stress (no relaxation) and compressive stresses in systole, which would decrease their longevity.

The compressive stresses shown in the Table are of only theoretical importance because they have been calculated using the image of stress-strain curves in the compressive stress region.

Natural leaflets and bioprosthetic leaflets cannot sustain compressive stresses; therefore, the stress-strain curve in the compressive stress region cannot be determined. It is for this reason that a tendency to produce compressive stresses would cause structural failure of the leaflet. Compressive stress occurs as a result of increased bending stress. The bending stress can be decreased by reducing the thickness (T) or the elastic modulus (E) (equations 1 and 2). A reduction of the thickness, however, will increase the membrane stress, thereby increasing the total stress to a dangerously high value. The reduction of the elastic modulus will reduce bending stress and also total stress. However, this reduction will increase the change in the leaflet length from systole to diastole, thereby making the leaflet susceptible to fatigue failure. Thus, it is evident that the natural leaflet has desirable values of thickness and elastic modulus. A major deviation from these specifications could cause premature failure of aortic valve leaflets.

Acknowledgment

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The Use of Time-Interrelated Covariates to Predict Survival Following Aortic Valve Replacement

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David R. Thomas, Ph.D., John M. Luber, M.D., Louis E. Lambert, M.S.,
Yuen-Fure Suen, M.S., and Albert Starr, M.D.

ABSTRACT **One hundred four patients survived isolated aortic valve replacement with the model 1200 prosthesis between 1965 and 1968, with a 12-year survival of 64%. Multiple regression survival analysis was employed in an attempt to determine which of 26 preoperative variables affected late survival and to devise a formula to predict survival for a given individual. The most important variables in the regression equation were right atrial mean pressure, etiology, and sex. The effect of the last two were found to vary with time over the 12-year postoperative period. An extension of the standard regression analysis technique was developed to incorporate time-related cofactors into the model. Based on the multiple regression model, 12-year survival was estimated to range from 92% to 14% for the best and worst combinations, respectively, of the three significant variables. The advantages of the regression method are outlined and the findings of other studies with regard to factors affecting survival after aortic valve replacement are summarized and discussed.**

Late survival after aortic valve replacement appears to be relatively independent of the type of prosthesis used [8], but greatly influenced by various patient-related variables [1, 2, 4–6, 10, 12, 13]. The determination of such variables is of obvious importance not only in providing an accurate prognosis for the patient but also in allowing the physician to make intelligent choices as to which patients are most likely to benefit from aortic valve replacement. The first step toward elucidating the effects of these variables is to examine the survival associated with different levels of each individual variable. Of more practical interest, however, is a multiple regression analysis, which takes into account their combined effect.

Material and Methods

From 1965 to 1968, 104 model 1200 non-cloth-covered prostheses were implanted in operative survivors [9]. These prostheses have a potential minimum follow-up of 10 years and thus provide an attractive data base for regression-type survival analysis. Accordingly, 26 preoperative clinical and diagnostic variables were obtained, and late survival was analyzed in relationship to these variables.

Late survival for the entire group and for the subsets defined by varying only one variable at a time was calculated according to the method of Kaplan and Meier [7]. Differences between subsets were tested for significance using the Mantel-Haenszel chi-square statistic [11].

In the multiple regression survival analysis described by Cox [3], the hazard function $h(t,x)$ associated with a given value of the prognostic variable x can be expressed as

$$h(t,x) = h_0(t) \exp(bx) \qquad (1)$$

where t represents postoperative time, exp is the exponential function, b is a regression coefficient whose value is estimated from the data, and $h_0(t)$, also estimated from the data, is the hazard function associated with the case $x = 0$. The estimates are derived by the maximum likelihood method. As can be seen from this equation, the hazard functions for different values of the parameter x are proportional to one another for all values of postoperative time.

The expression for the survival rate $P(t,x)$ at

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time t corresponding to the hazard function h(t,x) is

$$P(t,x) = P_0(t)^{\exp(bx)} \tag{2}$$

where $P_0(t)$ is the survival rate at time t for x = 0. Equation 2 implies that the survival rate functions or curves are all powers of one another. For example, if the risk due to a certain value of x is three times the risk associated with another value, then the survival rate at any postoperative time for the former situation will be the cube of the survival rate in the latter situation. An advantage of using the exponential function as the constant (or variable) of proportionality is that it remains non-negative without any restriction on the domain of definition of the covariate x or its coefficient b.

From a preliminary scan of the survival curves from the present study, it was seen that although a power relationship such as that implied by equation 2 was approximately true between different levels of some of the variables under consideration, other variables exhibited an interrelationship with time. This necessitated a refinement of the model. Cox [3] suggested a method for expanding the regression model to take into account such an interaction between postoperative time and the effect of a covariate. The relationship between the hazard functions becomes

$$h(t,x) = h_0(t)\exp(bx + b^*tx) \tag{3}$$

where the variable x is associated with two coefficients to be estimated, b and b*. The first (b) can be thought of as the intercept and the second (b*) as the slope of the relationship between postoperative time and the effect of variable x on survival. The significance of each can be tested separately. If the "intercept" is significantly non-zero and the "slope" is not, the model reduces to that expressed in equation 1. When the slope is significantly non-zero, however, no simple power relationship, such as that expressed in equation 2, exists between the survival curves for various values of x.

Results

One hundred four patients operated on for isolated aortic valve replacement with the model 1200 non-cloth-covered prosthesis from 1965 to 1968 survived the operation. Thirty-five patients died late, for a 12-year late survival of 64% (Fig 1). Twenty-six (74%) of these deaths were either valve-related, heart-related, or "sudden," and no information was available on the cause of 3 deaths (9%). As of this review,

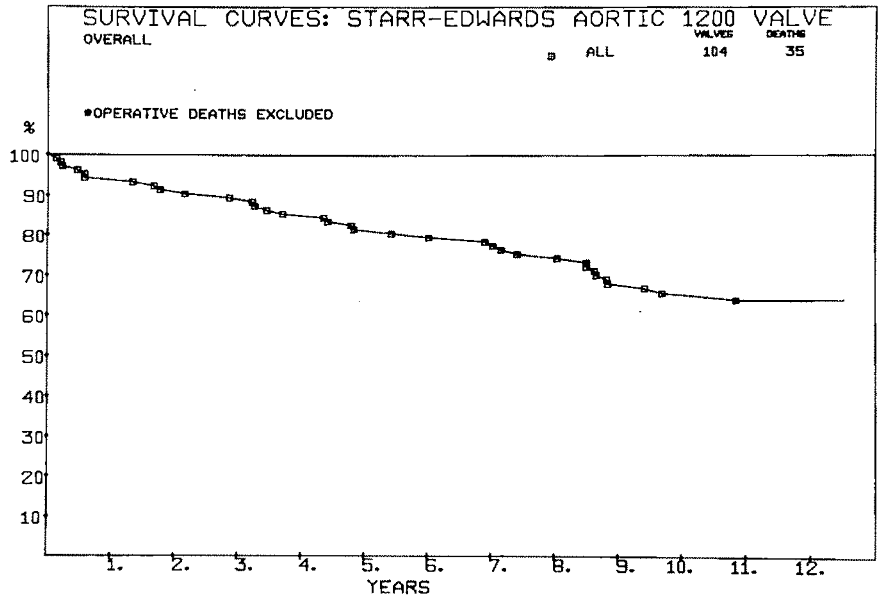


Fig 1. Survival curve for all 104 operative survivors of isolated aortic valve replacement with the model 1200 non-cloth-covered prosthesis from 1965 to 1968.

Table 1. Clinical Profile of 104 Operative Survivors and Relationship to Late Survival

Variable	Category	No. of Patients
Right atrial mean pressure[a] (mm Hg)	0–5	58
	6–10	12
Etiology = calcific degenerative[b]	Yes	56
	No	48
Sex[b]	Male	75
	Female	29
Aortic regurgitation[b]	Yes	63
	No	41
Aortic systolic pressure[c] (mm Hg)	45–120	33
	121–235	40
LV hypertrophy by ECG	Yes	85
	No	18
Right heart failure (clinical)	Yes	11
	No	93
Age (yr)	19–49	36
	50–59	34
	60–75	34
Syncope	Yes	27
	No	77
Angina	Yes	71
	No	33
Duration of angina (mo)	1–12	27
	13–400	44
Congestive heart failure	Yes	61
	No	42
Duration of congestive heart failure (mo)	1–12	28
	13–132	33
Previous embolus	Yes	8
	No	96
Previous infarction	Yes	9
	No	95
Previous aortic valve replacement	Yes	6
	No	98
NYHA Functional Class	I	1
	II	43
	III	49
	IV	11
Aortic stenosis	Yes	80
	No	24
RV systolic pressure (mm Hg)	20–30	24
	31–75	47
RV diastolic pressure (mm Hg)	0–5	48
	6–12	23
LV systolic pressure (mm Hg)	100–200	35
	201–325	35
LV diastolic pressure (mm Hg)	0–10	30
	11–45	39
Aortic diastolic pressure (mm Hg)	15–60	35
	61–105	38
Aortic valve gradient (mm Hg)	0–50	23
	51–200	48
Cardiac index (L/min/m^2)	1.5–2.4	32
	2.5–4.4	36
Valve size (mm)	21	27
	22	29
	24	20
	26	21
	27	7

[a]$p < 0.01$. [b]$p < 0.05$. [c]$p < 0.10$. All p values are based on individual Mantel-Haenszel [11] test of significance.

LV = left ventricular; ECG = electrocardiogram; NYHA = New York Heart Association; RV = right ventricular.

the operative survivors had accumulated 866 patient-years of follow-up (mean, 8.2 years), representing 96% of the follow-up possible if all living patients had been accounted for.

Twenty-six preoperative variables are listed in Table 1 in the order of the significance of their influence on late survival. Four were significant at the 5% level: right atrial mean pressure (Fig 2), etiology (Fig 3), sex (Fig 4), and the presence of aortic insufficiency. Three of these variables were also significant at the 5% level in the regression model, and none of the other variables entered the regression model at the 10% level. The variable sex contributed two coefficients to the model: b_1 ($p = 0.002$), which was positive, and b_1^* ($p = 0.007$), which was negative, indicating a lessening of the effect of sex with increasing postoperative time. This effect can be seen in Figure 4 as an early separation between the survival curves for men and women, with a gradual decreasing of the difference over time. Etiology contributed a single coefficient, b_2^* ($p = 0.004$). This coefficient was positive, indicating an increasing effect of the influence of calcific degenerative etiology over time. Right atrial mean pressure entered the model with a single positive coefficient b_3 ($p = 0.020$), indicating that increased pressure was associated with lower survival and that proportionality provides a satisfactory representation of the relationship between the hazard functions for different levels of that variable. Thus the complete model, in terms of the hazard function, is

$$h(t,x_1,x_2,x_3) = h_0(t)\exp(b_1x_1 - b_1^*tx_1 + b_2^*tx_2 + b_3x_3) \quad (4)$$

A computational maneuver involving a dummy variable to indicate the presence of a value for right atrial pressure was employed, but is suppressed in equation 4 for simplicity of presentation. It is seen from equation 4 that postoperative time (t) enters the exponential argument twice: once in connection with variable x_1 (sex) and once in connection with variable x_2 (etiology). The values of the predictive variables for 5 typical patients together with their survival curves are presented in Figure 5. It can be seen that these curves are not simple powers of one another.

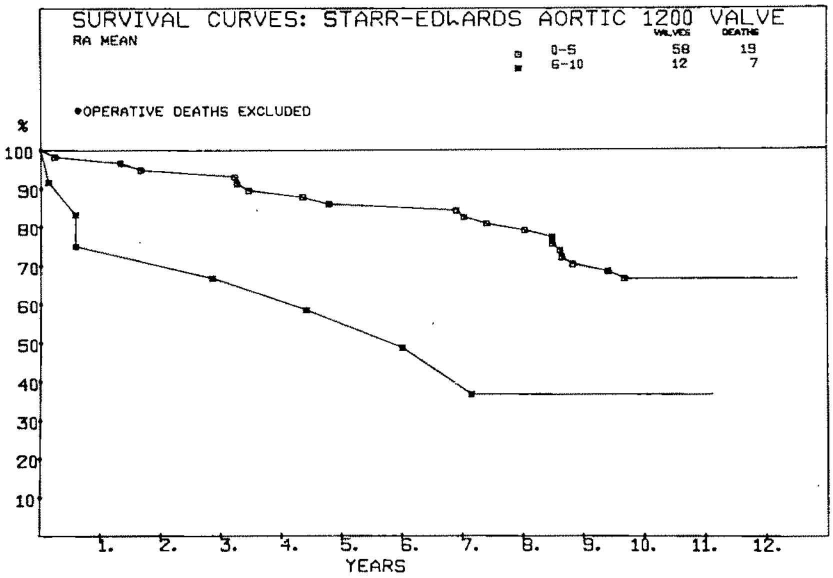


Fig 2. Late survival related to right atrial (RA) *mean pressure.*

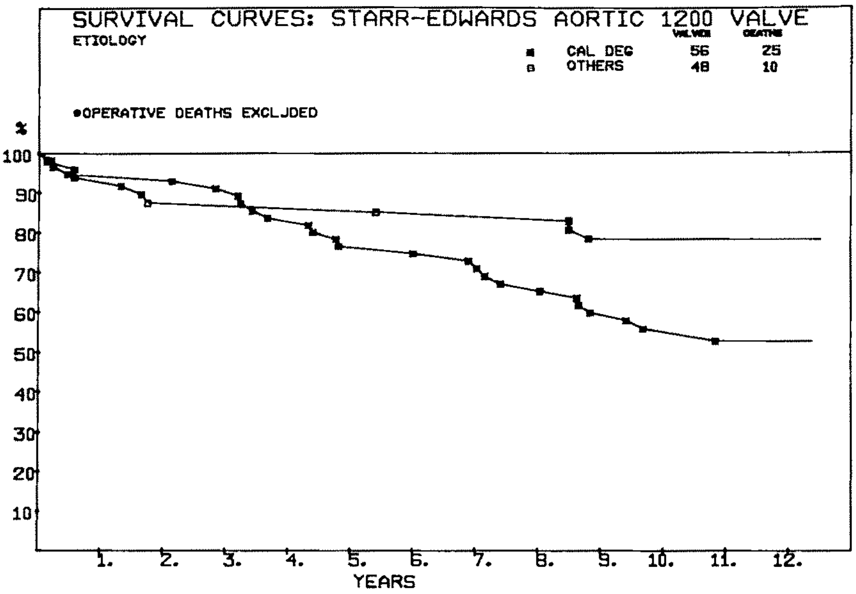


Fig 3. Late survival related to etiology of the aortic valve disease. (CAL DEG = *calcific degenerative.)*

Comment

Survival following aortic valve replacement has been shown to be influenced by various preoperative variables. Multiple regression survival analysis takes into account the influence on survival of several preoperative variables acting simultaneously. An advantage of using a regression model is that data from all the patients in the series are used to construct an equation from which survival estimates for any particular subset of patients can be made. The alternate approach is to base survival estimates for a given subset on only those patients from the series who fall into that particular category. This results in a loss of precision because of the resulting small sample sizes. For example, the categories illustrated in Figure 5 actually contained sample sizes that ranged from only 5 (E) to 29 (C) patients, whereas the total group of 104 patients was used to construct each of the curves corresponding to the 5 typical patients.

The reason for using the model 1200 valves to

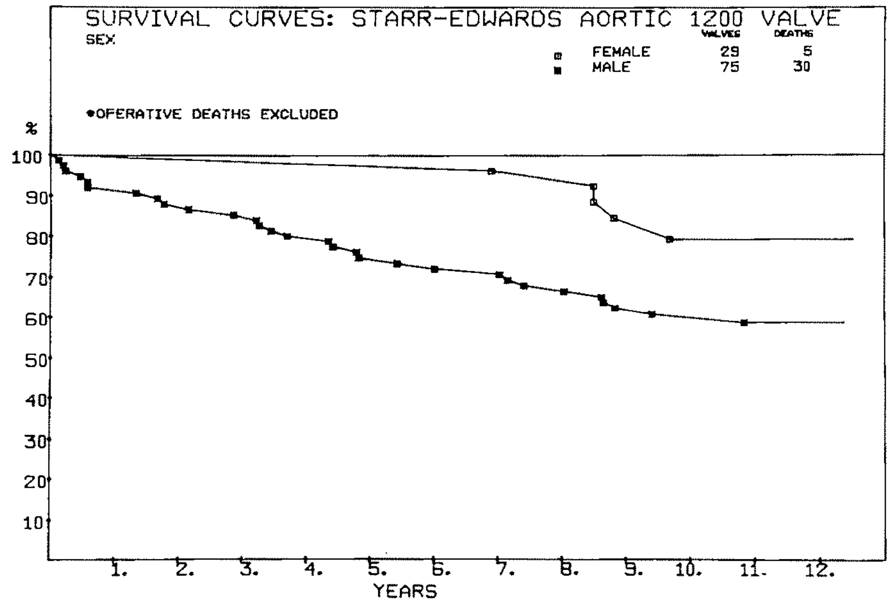
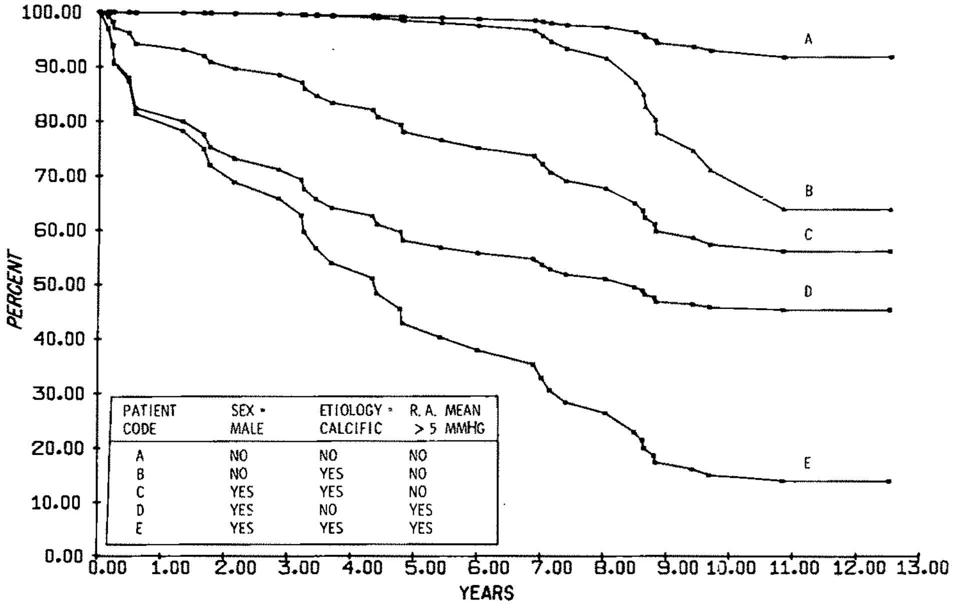


Fig 4. Late survival related to sex of the patients.



PATIENT CODE	SEX = MALE	ETIOLOGY = CALCIFIC	R. A. MEAN > 5 MMHG
A	NO	NO	NO
B	NO	YES	NO
C	YES	YES	NO
D	YES	NO	YES
E	YES	YES	YES

Fig 5. Survival curves for 5 typical patients from the regression model. Using the regression method, information from all 104 operative survivors is utilized to estimate the survival for a patient with the given set of characteristics, even though the number of patients actually possessing those characteristics is much smaller.

demonstrate the regression method was that each valve had a potential follow-up of at least 10 years. However, a disadvantage of using this series is that several factors related to the procedure (e.g., operative techniques, postoperative medical management) may have changed to such a degree during the last decade that the curves in Figure 5 may not be representative of those obtainable in current practice. More importantly, many potentially valuable diagnostic variables (e.g., left ventricular volumes and mass, coronary artery anatomy) were not available during the years in which this series was implanted. Nevertheless, the series provides good material for demonstrating the statistical methodology.

Table 2 contains a summary of the effect of given variables on survival as reported in vari-

Table 2. Comparison of Variables Found to Affect Survival after Aortic Valve Replacement (See Comment)

Variable	Present Study (N = 104)	Refs 1, 4 (N = 548[a])	Ref 2 (N = 1127[a])	Ref 5 (N = 191[a])	Ref 6 (N = 163)	Ref 10 (N = 314)	Ref 12 (N = 95)	Ref 13 (N = 212)
Functional Class	O	X	X	X[b]	X	. . .	X	X
Lesion (AS,AI)	X	O	X	. . .	O	X	O	X
Cardiothoracic ratio	. . .	X	X	O	X	. . .	. . .	. . .
Sex	X	O	O	X	. . .	O	. . .	. . .
Age	O	O	X	O	. . .	X	. . .	. . .
Cardiac index	O	. . .	X	O	. . .	. . .	O	X
LV hypertrophy	O	X	O	X	. . .	. . .	. . .	. . .
LA mean pressure	. . .	. . .	X	X	. . .	. . .	. . .	. . .
PA mean pressure	. . .	. . .	X	X	. . .	. . .	. . .	. . .
Heart failure	O	O	X	O	. . .	. . .	O	. . .
Valve size	O	X	. . .	. . .	O	. . .	. . .	. . .
Etiology	X	. . .	. . .	. . .	. . .	. . .	. . .	O
Previous infarction	O	. . .	X	. . .	. . .	. . .	. . .	. . .
LV diastolic pressure	O	. . .	. . .	X	. . .	. . .	O	. . .
RA mean pressure	X	. . .	. . .	. . .	. . .	. . .	. . .	. . .
LV dysfunction	. . .	. . .	X	. . .	. . .	. . .	. . .	. . .
Coronary disease	. . .	. . .	X	. . .	. . .	. . .	. . .	. . .
Angina	O	O	O	O	. . .	. . .	X	. . .

[a] Operative deaths included in analysis.

[b] AS patients only; other x's in this column refer to AI only.

X = finding of a significant difference; O = failure to find significant difference; AS = aortic stenosis; AI = aortic insufficiency; LV = left ventricular; LA = left atrial; PA = pulmonary artery; RA = right atrial.

ous clinical studies. Included in this table are only those variables found to have a significant effect on survival (by the nonregression approach) in at least one study. For example, of the 18 variables in the list, Isom and associates [6] tested 4 and found 2 (functional class and cardiothoracic ratio) to affect survival significantly. Copeland and colleagues [2] found a separate set of variables that significantly affected the survival of patients with stenosis and insufficiency.

No clear picture emerges from Table 2 concerning the relationship between these variables and their effect on survival. Although most studies of this type find certain variables to have a significant effect on survival, few agree exactly as to which precise combination of variables is important. Contributing to this problem is the fact that when multiple tests of significance are performed on the same data set, the probability of finding spurious significance is increased. As a consequence, the *p* values found in most studies of large numbers of variables should not be interpreted literally but only as a measure of relative magnitudes.

Some of the variability in findings among various studies is contributed by correlative interrelationships among the variables themselves. The significance attributed to a given variable may be only secondary to that of another, or conversely, truly important variables may fail to appear so because of a negative correlation with another variable. The regression approach overcomes these problems by judging the importance of each variable in light of all the other variables, thus ensuring that no important variables remain undiscovered and eliminating variables whose influence is secondary to other more important variables. The regression approach also permits an overall summary of the simultaneous influence of the important variables in terms of a single, individualized survival curve for a given patient (see Fig 5), rather than several separate curves (see Figs 2–4) whose interrelationship is otherwise impossible to determine.

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A candidate applying for admission to the 1982 certifying examination must fulfill all the requirements for the Board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, 14640 E Seven Mile Road, Detroit, MI 48205.

Considerations in Selection and Management of Patients Undergoing Valve Replacement with Glutaraldehyde-Fixed Porcine Bioprostheses

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John W. Kirklin, M.D., Nicholas T. Kouchoukos, M.D., Albert D. Pacifico, M.D.,
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Steven Piantadosi, M.D., and Edwin L. Bradley, Ph.D.

ABSTRACT **From November, 1973, through June, 1978, 428 operations in 425 patients were performed for replacement of aortic, mitral, or aortic plus mitral valves, utilizing 277 Hancock and 180 Carpentier-Edwards bioprostheses. Actuarially determined survival at 36 months was similar for all three groups and compared favorably with our experience with the Björk-Shiley prosthesis. Certain patient-related variables influencing late survival were identified by multivariate analysis and included previous operation for congenital heart disease, coronary artery bypass grafting in nonaortic valve replacement, race (black), age at operation, and New York Heart Association Functional Class. A small but definite incidence of thromboembolism occurred in all three groups, again similar to our experience with the Björk-Shiley prosthesis. Multivariate analysis identified four factors influencing risk of thromboembolism: previous cardiac operation, age, double-valve replacement, and rhythm at discharge. Valve degeneration occurred, primarily in children and young adults. Over the medium term, the porcine bioprosthesis compared favorably with mechanical prostheses in terms of survival, function, and thromboembolism. Certain patient-related variables affecting survival may be modified by earlier surgical intervention.**

The ideal cardiac valve substitute has yet to be developed. As the result of efforts to circumvent the well-known hazards associated with mechanical valvular replacement, development of the glutaraldehyde-fixed, flexible stent-mounted porcine bioprosthesis has produced a product of well-documented medium-term durability and low thrombogenicity. It can be used under most circumstances without the attendant risks of anticoagulation [1, 7, 15].

After fifteen years of clinical use, major questions that remain concerning the porcine bioprosthesis include its long-term durability, its use in children and young adults, the actual incidence of thromboembolism, and its use in patients for whom long-term anticoagulation will be necessary.

Material and Methods

From November, 1973, through June, 1978, 428 operations for the replacement of aortic, mitral, or aortic plus mitral valves were performed in 425 patients at the University of Alabama in Birmingham utilizing 277 Hancock and 180 Carpentier-Edwards bioprostheses (Table 1). Implantation of Carpentier-Edwards bioprostheses began in March, 1977. Specifically excluded from this analysis were patients undergoing operation utilizing valved conduits or bioprostheses fixed in formalin or mounted on rigid stents, and those undergoing mixed valvular replacement with mechanical devices and porcine bioprostheses.

Of the 425 patients in the study, 21 died in the first 30 days after operation, and no follow-up after 30 days was available for 9 patients. This left 395 patients for whom follow-up of more than 30 days was possible. Two hundred sixty-four were males and 131, female. There were 286 whites, 108 blacks, and

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Table 1. Thirty-Day Mortality After Implantation of Porcine Bioprostheses

Procedure	No. of Procedures	30-Day Mortality (No. of Patients)
AVR	205	8/285 or 2.8%
AVR + assoc. procedure	82	
MVR	82	10/111 or 9.0%
MVR + assoc. procedure	29	
AVR + MVR	27	3/29 or 10.3%
AVR + MVR + assoc. procedure	3	
Total	428[a]	21[b]

[a] In 428 operations in 425 patients, 457 bioprostheses were used: 277 Hancock and 180 Carpentier-Edwards.

[b] After 30 days, 21 patients had died and no follow-up was available on 9. Therefore, the total number of patients reviewed for this study was 395. The total number of operations included was 398.

AVR = aortic valve replacement; MVR = mitral valve replacement.

1 Oriental. Mean age was 50.2 years (range, 1.3 to 84.7 years). Three of the 395 patients were operated on twice during the study period, bringing the total number of operations considered in this analysis to 398.

Valves were replaced using conventional techniques of cardiopulmonary bypass [13]. Associated procedures included coronary artery bypass grafting (74 procedures), concomitant valvuloplasty (26), repair of congenital defect (17), and replacement of the ascending aorta (6). Three types of myocardial preservation were utilized: coronary perfusion (16 procedures), cold ischemic arrest (189), and cold multidose potassium cardioplegia (193) [5].

Valves were inserted using three suture techniques: continuous Prolene (49 valve insertions), simple interrupted (183), or pledgeted mattress (183). In 7 instances the suture technique could not be determined from the operative note. When indicated, the aortic root was enlarged to accommodate a larger bioprosthesis.

Selected patients were discharged on a regimen of anticoagulant therapy, begun as orally administered dicumarol on the second postoperative day. In general, it was discontinued after 6 to 12 weeks, but in 10 patients was continued over the long term.

The follow-up period extended through March, 1979. Follow-up was achieved by letters to patients, letters to referring physicians, or direct patient contact by telephone or office visit. When follow-up could not be initiated, the last time the patient was seen by one of us was used as the follow-up date.

Among late survivors for whom follow-up of longer than 30 days was available, the median duration of follow-up was 19.1 months (range, 1.5 to 62.2 months). For the group of patients undergoing aortic valve replacement, median follow-up was 18.5 months (range, 1.5 to 62.2 months); for mitral valve replacement, 23.5 months (range, 4.5 to 60.5 months); and for aortic plus mitral valve replacement, 33.0 months (range, 7.2 to 58.2 months).

Definitions

The following definitions were applied throughout the study:

Study group: all patients undergoing aortic, mitral, or aortic plus mitral valve replacement with a porcine bioprosthesis manufactured by Hancock or Edwards Laboratories

Porcine bioprosthesis: porcine valve, fixed in glutaraldehyde, mounted on metal (Carpentier-Edwards) or plastic (Hancock) flexible stents

Major thromboembolic event: an event characterized by definite or highly suggestive evidence of limb, visceral, or cerebral ischemia occurring suddenly, and not resolving completely within twenty-four hours

Minor thromboembolic event: transient visceral or neurological event, which resolved without sequelae within twenty-four hours

Bioprosthesis degeneration: calcification, fibrosis, thickening, stiffening, or degeneration of intrinsic porcine valve tissue, excluding parabioprosthetic leak, resulting in reoperation or death

Unstable atrial rhythm: atrial fibrillation, flutter, or tachycardia present at discharge, exclusively or in conjunction with periods of normal sinus rhythm

Statistical Analysis

The events of late death, late cardiac death, and first episode of thromboembolism were analyzed by the reduced sample actuarial method [2] and valve degeneration, by the product limit method [11]. The uncertainty of actuarial point estimates are presented using 70% binomial confidence limits, using the calculated standard error to obtain an effective sample size. Estimates are plotted from 100% event-free at 30 days. Factors affecting the risk of late events were then identified using Breslow's [3] formulation of the Cox [6] proportional hazards general linear model: relative hazard $= \exp(\lambda_1 x_1 + \lambda_2 x_2 + \ldots + \lambda_k x_k)$, where x_i are the risk variables, λ_1 are the estimated hazard parameters,* which when multiplied by x_i yields a risk coefficient, and the relative hazard refers to the risk to patients not yet experiencing the event in question when the risk factor is present. The analyses of death and cardiac death were carried out separately in the aortic and mitral valve replacement groups, but not in the double-valve group due to low numbers (4 deaths in 25 patients).

We subsequently used these separate analyses to build an overall model that included certain factors (those factors with $p < 0.2$) uniquely associated with only one or two of the three groups (interaction terms). Each factor identified was examined to ascertain its frequency of occurrence or distribution relative to the event in question. In some instances, factors were not kept in the model because the factor applied to only a small number of patients (e.g., 6 to 8 patients) and the event occurred at increased frequency in these few patients. We choose to call these "spurious" for the time being.

The factors examined included demographic variables (age, sex, race, Veterans Administration Hospital patients), preoperative variables (previous valve replacement, previous operation for congenital heart disease or any previous heart operation, New York Heart Association [NYHA] Functional Class), operative variables (valve replaced, manufacturer of the bioprosthesis, size of the bioprosthesis, technique of bioprosthesis insertion—simple interrupted, continuous, or pledgeted mattress—use of coronary artery bypass grafting, technique of myocardial protection, aortic cross-clamp time), and the postoperative variable of cardiac rhythm at the time of discharge from the hospital (sinus, atrial fibrillation, other). Quantitative variables are presented as mean ± 1 standard error.

Results

Survival

There were 44 late deaths; all but 12 were from cardiac causes. Cardiac causes of death included the following: sudden death, 15 patients; paravalvular leak, 3; cerebrovascular accident, 3; myocardial infarction, 3; congestive heart failure, 2; subacute bacterial endocarditis, 2; aortic dissection, 2; degeneration, 1; and cardiomyopathy, 1. The noncardiac causes of death were as follows: chronic liver or renal failure, 4 patients; sepsis, 2; pneumonia, 2; carcinoma, 2; and unknown, 2. Late survival was similar for aortic, mitral, and aortic plus mitral valve replacement subgroups. Actuarial survival at 36 months for aortic valve replacement was 87%, CL* 84%–90%; for mitral valve replacement, 82%, CL 76%–87%; and for aortic plus mitral valve replacement at 30 months, 78%, CL 63%–89% (Fig 1A). Comparison with our Björk-Shiley [12] experience for aortic and mitral valve replacement is shown in Figure 1B and C.

Late survival was also influenced by the preoperative NYHA Functional Class (Fig 2).

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*We have employed for this estimation a computer program written by Frank Harrell, Jr., Ph.D, at Duke University and interfaced to the Statistical Analysis System.

*CL refers here and elsewhere to 70% binomial confidence limits, roughly equivalent to ± 1 standard error.

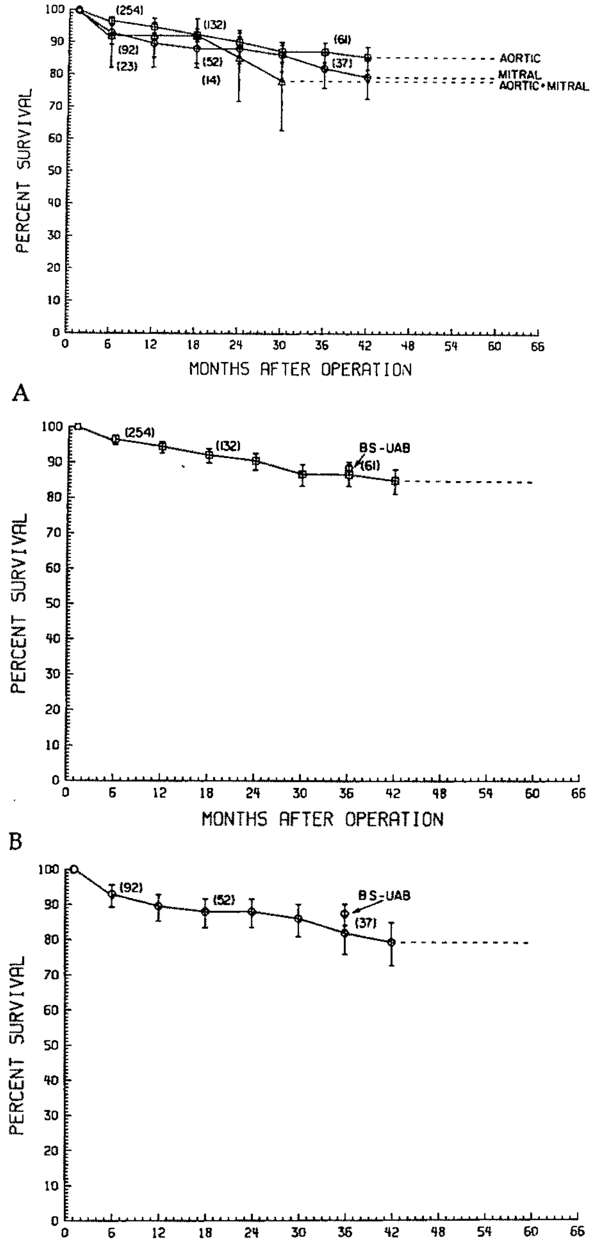


Fig 1. (A) Late survival by operation for patients undergoing aortic, mitral, and aortic plus mitral valve replacement with a bioprosthesis. Survival in (B) aortic and (C) mitral valve groups in this series is compared with our series of Björk-Shiley (BS-UAB) *patients* [12]. *Vertical bars represent 70% confidence limits.*

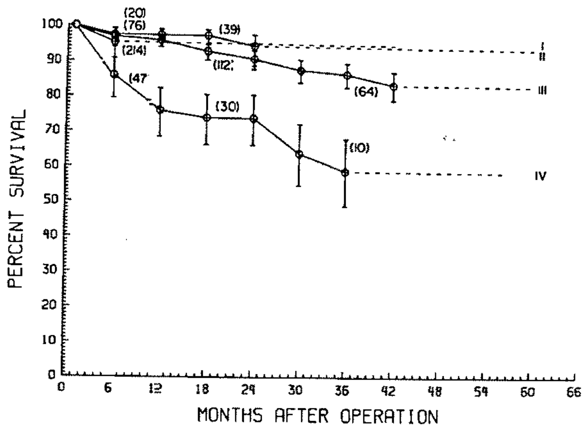


Fig 2. Survival by preoperative New York Heart Association Functional Class for all groups. Vertical bars represent 70% confidence limits.

Actuarial survival at 36 months for all groups in NYHA Class I was 95%, CL 85%–99%; for Class II, 94%, CL 89%–97%; for Class III, 87%, CL 83%–90%; and 59% for Class IV, CL 49%–68%.

The results of the multivariate analysis of all causes of late death are shown in Table 2. Two of 7 patients with previous operation for congenital heart disease died (29% versus 11% of the remaining patients). The increased risk with coronary artery bypass grafting was most apparent in those patients having mitral valve replacement (5 out of 13 or 38% versus 11% in the remaining mitral group) as opposed to aortic valve replacement (6 out of 55 or 11% versus 9% in the remaining aortic group). This is reflected in the adjustment "interaction term" of coronary artery bypass grafting (negative sign in the tabulated coefficient for "aortic valve replacement only"). The influence of being black was also most prominent in the mitral valve replacement group (7 out of 32 or 22% versus 12% in the remaining mitral group) as opposed to the smaller difference in the group having aortic valve replacement (8 out of 62 or 13% versus 8% in the remaining group). Older age increased risk, the average age at operation for patients still alive being 50 ± 1.0 years versus 55 ± 2.8 for those dying (p = 0.11). New York Heart Association Functional Class influenced survival, the mean preoperative class for those still alive being 2.77 ± 0.039 versus 3.30 ± 0.108 for those dying ($p < 0.0001$). The patients seen early in the series in whom coronary perfusion was used were at increased risk, 3 out of 16 (19%) having died as opposed to 41 out of 382 (11%) of the remaining patients. We did not find by multivariate analysis that sex, position of valve replacement, bioprosthetic device, manufacturer, technique of insertion, ischemia

Table 2. Multivariate Analysis of the Risk of Late Death from All Causes (44 Events)

Variable (X)	Coefficient (λ) (± SD)[a]	p Value	Relative Risk (± SD)[b] Adjusted for All Factors
Previous operation CHD	3.4 ± 0.93	= 0.0003	29 (11–72)
CABG	1.7 ± 0.48	= 0.0006	5.3 (3.3–8.6)
Adjustment for AVR only	−1.2 ± 0.59	= 0.04	1.6[c]
Black	1.4 ± 0.43	= 0.0015	3.9 (2.6–6.0)
Adjustment for AVR only	−0.8 ± 0.52	= 0.13	1.8[c]
Age (yr)[d]	0.033 ± 0.0110	= 0.003	. . .
NYHA Functional Class[d]	0.7 ± 0.26	= 0.0045	. . .
Coronary perfusion	1.2 ± 0.68	= 0.07	3.4 (1.7–6.7)

[a] If more than one factor is present, the coefficients must be added and the result exponentiated to obtain the relative risk.
[b] The exponentiated value of individual coefficients.
[c] In AVR, the increased risk of being black or having had CABG is not apparent, the relative risk coefficient being expressed for this group as the algebraic sum of the coefficients applicable.
[d] Multiply by age in years or NYHA Class to obtain the risk coefficient.

CHD = congenital heart disease; CABG = coronary artery bypass grafting; AVR = aortic valve replacement; NYHA = New York Heart Association.

Table 3. Multivariate Analysis of the Risk of Late Death from Cardiac and Unknown Causes

Variable (X)	Coefficient (λ) (± SD)[a]	p Value	Relative Risk (± SD)[b] Adjusted for All Other Factors
Previous operation CHD	3.6 ± 0.95	< 0.0001	38 (15–98)
Black	1.7 ± 0.53	= 0.001	5.7 (3.4–9.6)
Adjustment for AVR only	−1.4 ± 0.68	= 0.04	1.4[c]
Age (yr)[d]	0.026 ± 0.0121	= 0.03	. . .
NYHA Functional Class[d]	0.6 ± 0.27	= 0.02	. . .
Coronary perfusion	1.3 ± 0.72	= 0.08	3.5 (1.7–7.2)
If *not* isolated AVR, CABG	2.4 ± 0.56	< 0.0001	11 (6–19)
If isolated AVR, Male	1.0 ± 0.50	= 0.05	2.7 (1.7–4.5)

[a] If more than one factor is present, the coefficients must be added and the result exponentiated to obtain the relative risk.
[b] The exponentiated value of individual coefficients.
[c] In AVR, the increased risk of being black or having had CABG is not apparent, the relative risk coefficient being expressed for this group as the algebraic sum of the coefficients applicable.
[d] Multiply by age in years or NYHA Class to obtain the risk coefficient.

CHD = congenital heart disease; AVR = aortic valve replacement; NHYA = New York Heart Association; CABG = coronary artery bypass grafting.

time, or discharge rhythm influenced the overall death rate.

The results of the multivariate analysis of deaths due to cardiac and unknown causes are shown in Table 3. Most factors are similar to those just mentioned since most deaths were from these causes. In this analysis, however, the factor coronary artery bypass grafting is important only in non-aortic valve replacement (p = 0.9 for the aortic group). In addition, being male was significantly less related to these causes of death in the aortic valve group (18 out of 203 or 9% versus 3% for females) as opposed to the mitral replacement group (9 out of 56 or 16% versus 8% for females).

Thromboembolism

The actuarial freedom from thromboembolism, both major and major plus minor, for all patients is depicted in Figure 3A. Freedom from major embolic events at the 36-month interval was 95%, CL 93%–97% and from all embolic events 90%, CL 87% to 92%. The actuarial freedom from all thromboembolic events for aortic

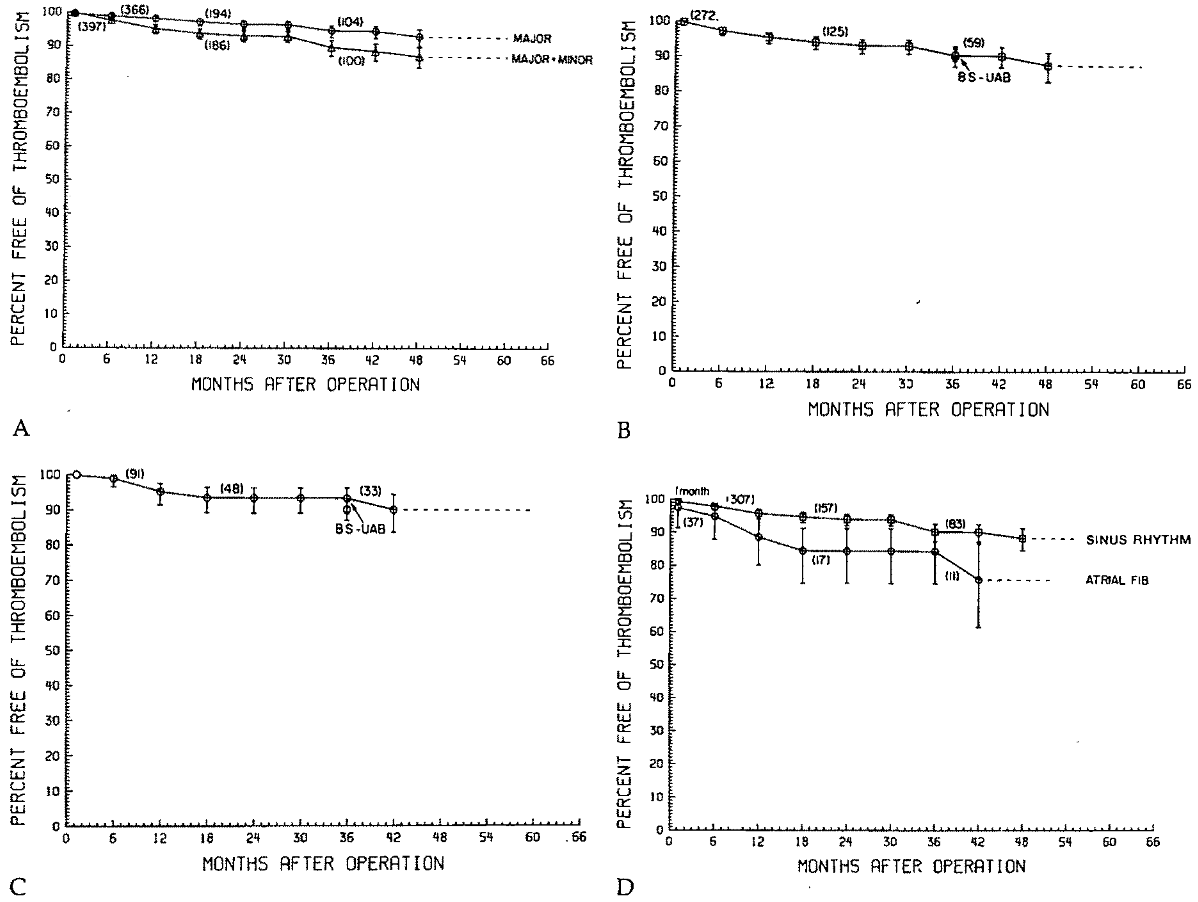


Fig 3. (A) Patients free from major or major and minor thromboembolic events. Patients in the (B) aortic and (C) mitral valve replacement groups are compared with our experience with the Björk-Shiley (BS-UAB) *prosthesis. (D) Comparison of freedom from all thromboembolic events in patients discharged in sinus rhythm and atrial fibrillation. Vertical bars represent 70% confidence limits.*

and mitral valve replacement is shown in Figure 3B and C, and is compared with our Björk-Shiley experience. For aortic valve replacement, actuarial freedom from emboli was 91%, CL 87%–93%, and for mitral valve replacement 93%, CL 89%–96%. The influence of rhythm at discharge is suggested in Figure 3D. At 36 months, for those patients discharged in sinus rhythm, actuarial freedom from emboli was 90%, CL 87%–92%, versus 84%, CL 74%–91% for those discharged in atrial fibrillation.

The results of the multivariate analysis of thromboembolism are in Table 4. Previous heart operation (congenital or acquired heart disease) was associated with an increased risk of thromboembolism (5 out of 38 or 13% versus 6% for all other patients). Patients who were older at operation had an increased risk, those having thromboembolism being 57 ± 3.1 years versus 50 ± 1.0 years for those with no thromboembolic event ($p = 0.05$). More thromboembolic events occurred in double-valve replacement (4 out of 25 or 16%) than in either aortic valve replacement (17 out of 273 or 6.2%) or mitral valve replacement (6 out of 100 or 6%). Patients in atrial fibrillation at discharge were at increased risk of thromboembolism (6 out of 38 or 16% versus 6% in the remaining patients). There was no demonstrated effect of valve manufacturer type on thromboembolism, nor could we demonstrate any increased risk of thromboembolism due to the type of suturing technique employed.

Bioprosthesis Failure

There were three known causes of bioprosthesis failure leading to reoperation or death in the follow-up period: parabioprosthetic leak (11

Table 4. Multivariate Analysis of the Risk of Late Thromboembolism

Variable (X)	Coefficient (λ) (± SD)[a]	p Value	Relative Risk (± SD)[b] Adjusted for All Other Factors
Any previous heart operation	1.5 ± 0.52	= 0.004	4.4 (2.6–7.4)
Age (yr)[c]	0.036 ± 0.0132	= 0.006	. . .
Double-valve replacement	1.3 ± 0.057	= 0.02	3.8 (2.1–6.7)
Atrial fibrillation	0.7 ± 0.48	= 0.15	2.0 (1.2–3.2)

[a] If more than one factor is present, the coefficients must be added and the result exponentiated to obtain the relative risk.
[b] The exponentiated value of individual coefficients.
[c] Multiply by age in years or NYHA Class to obtain the risk coefficient.

patients); degeneration (6); and thrombosis (1). In 2 patients, the cause was not known. Four of the parabioprosthetic leaks were the result of infection. The only instance of bioprosthesis thrombosis occurred on the fourth postoperative day in a patient undergoing mitral valve replacement with a Carpentier-Edwards bioprosthesis. This event resulted in death.

During the study and follow-up period, 5 patients underwent reoperation and re-replacement of the porcine bioprosthesis for degeneration. One additional patient died without reoperation. Subsequent to the follow-up period, an additional 3 patients have required reoperation for bioprosthetic degeneration. The mean duration of implantation for all degenerated bioprostheses was 46.3 months. All were Hancock bioprostheses (see Comments). Seven were in the mitral position; 2 were in the aortic. Eight were severely calcified or had undergone marked degeneration, and 1 had undergone spontaneous cusp rupture.

Actuarial incidence for degeneration in the entire group and for those less than 30 years old (86 bioprostheses in 77 patients) is shown in Figure 4. The results of multivariate analysis of bioprosthesis degeneration revealed the most important factor to be young age. The mean age for patients in whom degeneration occurred was 13 ± 3.1 years versus 51 ± 1.0 ($p < 0.0001$) for all other patients.

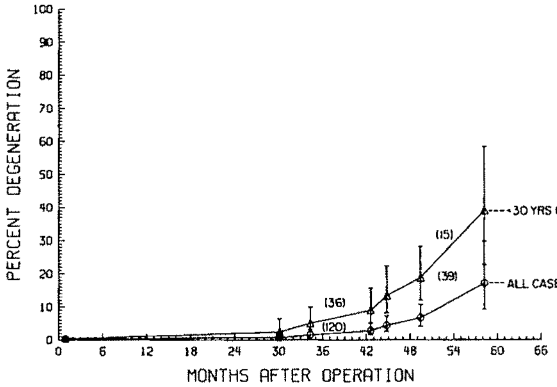


Fig 4. Actuarial incidence of bioprosthesis degeneration in all patients and in those less than 30 years old at the time of implantation. Vertical bars represent 70% confidence limits.

Improvement in Functional Class

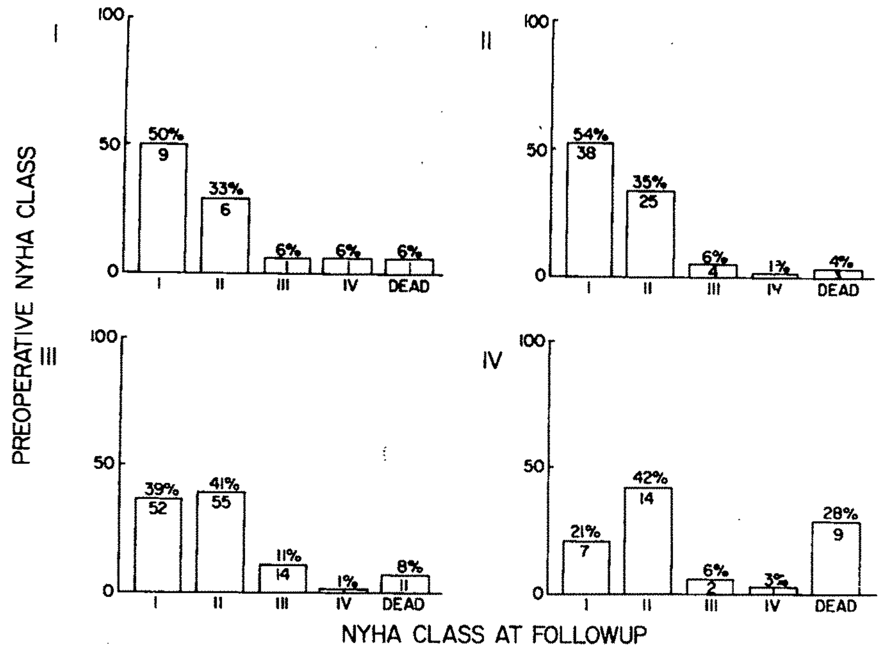
Comparison of preoperative and postoperative NYHA Functional Class for those patients in whom follow-up information was available for aortic, mitral, and aortic plus mitral valve replacement is noted in Figure 5. Improvement from Functional Classes III and IV preoperatively to Class I or II postoperatively occurred in 77% of aortic (CL 73%–81%), 67% of mitral (CL 61%–73%), and 65% (CL 51%–77%) of aortic plus mitral valve replacement patients.

Comments

Survival

Late survival is a function of multiple factors, both device-related and patient-related. Actuarial survival, which is a cumulative reflection of these variables, in this group of patients is no different at 36 months from that reported by Oyer [15], Angell [1], Davila [7], Cohn [4], and their associates.

It is apparent that such device-related variables as hemodynamic function, freedom from thromboemboli, freedom from complications of



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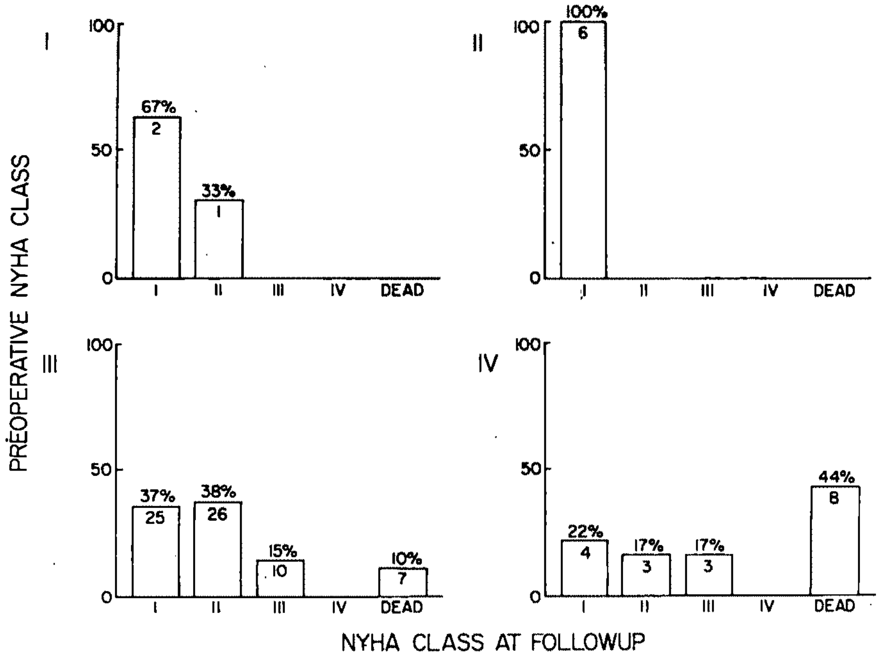

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anticoagulation, and durability all play a large part in patient survival following valve replacement. However, many other variables not related to the specific device also appear to determine survival. These include previous operation for congenital heart disease, coronary artery bypass grafting, race (black), age, NYHA Functional Class, and coronary perfusion.

Previous operation for congenital heart disease appeared as a significant risk factor in this analysis and could be due to the congenital lesion irrespective of the valve. Grunkemeier and associates [10, 16] noted, as did we in our Björk-Shiley study [12], that previous cardiac operation is a significant risk factor affecting survival. Previous valve replacement did not appear in this analysis, primarily because of the paucity of porcine bioprostheses selected for secondary valve replacement.

Coronary artery bypass grafting was an in-

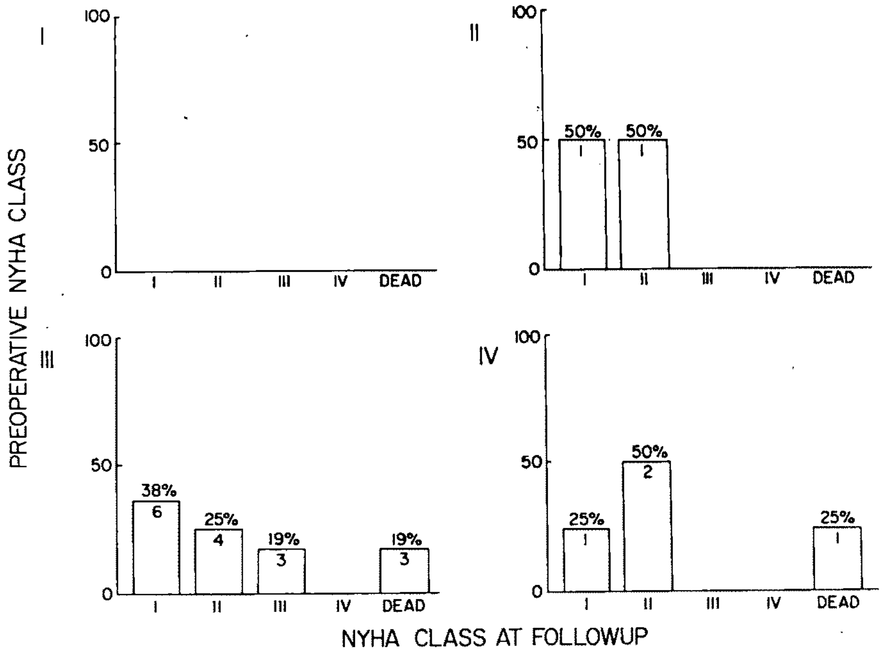

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Fig 5. New York Heart Association (NYHA) *Functional Class at follow-up for patients with (A) aortic, (B) mitral, and (C) aortic plus mitral valve replacement compared with preoperative class. Death is included and the total applies to the number of patients for whom adequate information was available.*

creased risk factor for late survival only in patients undergoing mitral and double-valve replacement. We do not have information as to the relative hazard of coronary artery disease left ungrafted in these patients. Four of 5 late deaths in the mitral group were patients who had valve replacement for papillary muscle dysfunction or ruptured chordae. Thus, valve replacement in these patients represents operation for ischemic myocardiopathy whereas bypass grafting in patients having aortic valve replacement is primarily for the relief of angina.

The significantly diminished survival noted in black patients is consistent with our similar observation in Björk-Shiley patients. The reasons for this are as yet unclear. The influence on survival of age and NYHA Functional Class most likely represent the functional state of the ventricle, which speaks for earlier intervention in valvular heart disease.

We believe the increased hazard to late survival of coronary perfusion reflects less satisfactory myocardial protection, although the effect may be related to duration of follow-up. Further clarification of this effect must await more definitive analysis of the effect of cold cardioplegia on long-term survival.

Thromboembolism

A major difference between this report and others is that only 10 of our patients were discharged on a regimen of long-term anticoagulation. By contrast, approximately 25% of the patients in the report of Angell and co-workers [1] and up to 33% of the patients having mitral or aortic plus mitral valve replacement in the study of Oyer and colleagues [15] were discharged on this regimen. Nonetheless, the incidence of thromboembolism reported by us is similar to theirs and is quite acceptably low. Our experience with patients receiving the Björk-Shiley prosthesis, all of whom are on a regimen of anticoagulants, showed a similar rate of thromboembolism. Thus, this series represents a "test" of the low thrombogenicity of the porcine bioprosthesis. It is important to note, however, that even in the aortic position, the porcine bioprosthesis is not totally free from thromboembolism.

Fairfax and associates [8] reported a twelvefold increase in risk of thromboembolic phenomena in patients with chronic sinoatrial disorder, and a fivefold increase in risk in patients with chronic atrial fibrillation with a slow ventricular rate as opposed to controls with complete heart block, thereby documenting significant risk with "unstable" atrial rhythm. In our group of porcine bioprostheses, multivariate analysis suggests that atrial fibrillation and thromboemboli are related, as does our actuarial analysis of incidence. Our concern is shared by Cohn and colleagues [4], who reported that as of 1979, all emboli in their series had occurred in patients in atrial fibrillation. The influence of age and previous cardiac operation is noted, but the mechanism is unclear. The risk associated with double-valve replacement is consistent with our findings in the Björk-Shiley report and suggests an additive effect of two devices in a single patient. It would seem that in situations when a need for long-term anticoagulation is demonstrated, a theoretical advantage of the porcine bioprosthesis is diminished. The limiting factor then becomes its durability.

Thrombosis and Degeneration

Thrombosis and bioprosthesis degeneration have been unusual events in our experience. However, thrombosis, when it occurs, whether it be in a prosthesis or bioprosthesis, is an almost uniformly fatal event. In our experience with the Björk-Shiley prosthesis, thrombosis occurred sixteen times (2.0%, CL 1.5%–2.7%) with a mortality of 81% (13 out of 16). When compared with thrombosis of porcine bioprostheses, the incidence was much less (0.2%, CL 0.4%–0.6% or 1 out of 457 bioprostheses at risk), but with a fatal result. However, a clear disadvantage of the bioprosthesis is degeneration, which occurred in this series in 6 patients during the follow-up period and in 3 patients subsequent to the follow-up period. In contrast to thrombosis in the Björk-Shiley series, only 1 patient died. Thus, in terms of ultimate patient salvage, patients with degenerated porcine bioprostheses fared better than patients with thrombosed Björk-Shiley prostheses.

Our multivariate analysis confirms that clearly the most important risk factor in degeneration is young age. Our experience is similar to that of Kutsche [14], Geha [9], and their coworkers and has become a major factor in our selection of valve substitutes in children.

As noted, all the degenerated valves were Hancock bioprostheses. A possible explanation for this finding may be the longer duration of implantation for all Hancock valves in the series (31 months versus 13 months for Carpentier-Edwards).

Hemodynamic Performance and Improvement in Functional Class

We have no direct evaluation of the hemodynamic characteristics of the porcine bioprosthesis in our population. Others [1, 4] have alluded favorably to the suitability and comparison with prosthetic devices. We recognize as reasonable evidence of satisfactory hemodynamics acceptable late survival and improvement in Functional Class. As noted, the improvement in preoperative Class III or IV patients to Class I or II postoperatively compares favorably with our experience with the Björk-Shiley prosthesis.

Conclusion

Prolonged survival with cardiac valve replacement is a result of many factors, both device-related and patient-related. When considering device-related factors, the porcine bioprosthesis compares favorably over the medium term with prosthetic devices. In spite of eliminating the morbidity associated with anticoagulants in the majority of patients, this report documents a small but definite incidence of thromboembolism, and suggests that durability may be limited, especially in younger subjects.

Ultimately, survival may be determined by patient-related factors present and operative at the time of valve replacement, such as previous cardiac operation, NYHA Functional Class, presence of coronary artery disease, age, and race. In our attempts to modify these patient-related factors, earlier surgical intervention may be the common denominator.

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Discussion

DR. LAWRENCE H. COHN (Boston, MA): It is always a pleasure to be a discussant of a well-presented paper with elegant statistical data. The authors have presented data on the single major advantage of the tissue valve: a low rate of thromboembolism when the patient is not on a regimen of anticoagulation. Very few of the patients in the series received anticoagulation, even if they were in atrial fibrillation, and the rate of thromboembolism is low. At the Peter Bent Brigham Hospital in Boston, we have been using the Hancock bioprosthetic valve since January, 1972, and, as of January, 1980, now have experience in about 750 patients. Our thromboembolic data support what Dr. Williams said about the cardiac rhythm; that is, atrial fibrillation seems to be an important factor in the determination of postoperative thromboembolic events in patients with bioprosthetic mitral valves.

In light of this morning's discussion about antiplatelet therapy, I thought these data might be of some interest. We surveyed 19 institutions that regularly use bioprosthetic mitral valves and found that a variety of anticoagulation regimens are currently employed, including the gradual introduction of aspirin and Persantine (dipyridamole) antiplatelet agents for patients with tissue valves. Obviously, there is still a great deal of information to be learned on this particular subject.

The authors have shown, as Don Magilligan did this morning, that there is a finite incidence of primary valve dysfunction of these valves correlated with time. Utilizing the sum of the single mitral valves and mitral valves from patients who have had double-valve replacement and charting these over time, we find that at the six-year mark, with a 95% confidence limit, the projected percent of valves dysfunction-free in our experience is 90%. In the sixth and seventh year of follow-up this percent drops off, but the numbers are considerably fewer and thus not statistically significant. Similarly, in the aortic valve group, again using the combination of isolated aortic valves and the valves from those patients who had double-valve replacement, the percent dysfunction-free at the five-year mark is 95%, with a 95% confidence limit.

My colleagues, Drs. Castenada and Norwood at the Boston Children's Hospital, have shown that in children with a mean age of less than 10 years, the incidence of porcine valve dysfunction from calcification is really quite high. It is now thought that this is not the valve to use in growing children since the probability of calcified valve at five years is very high indeed.

Finally, there are now some contradictions for bioprosthetic valve replacement: patients who have a very dynamic calcium metabolism, such as growing children, or those on renal dialysis who often have secondary hyperparathyroidism.

I have three questions for Dr. Williams. In our experience, we have about a two-thirds to one-third use of tissue versus prosthetic valves. Do you have data from your institution as to the relative percentages over the same time period, and, if so, what are your specific indications for the use of a tissue valve? Second, you reported that you used three suture techniques—running, interrupted, and mattress. Is there any difference in the incidence of perivalvular leaks following the use of any one of those techniques? Finally, can you venture an opinion regarding the advisability of using the tissue valve in a patient with active endocarditis, and, conversely, do you think it is more or less susceptible to postoperative endocarditis than the prosthetic valve?

DR. JURO WADA (Tokyo, Japan): At the Heart Institute of Japan, Hancock xenografts were implanted in the mitral position in 159 patients. The actuarial survival curve at four years was about 85%. In 130 adult patients, it was about 90% and in 20 children less than 15 years old, it was about 60%.

These results made me look more carefully into valve replacement in children. Between 1975 and 1978, 30 patients received 33 Hancock valves. Between 1971 and 1979, 14 children received a Björk-Shiley valve (total follow-up, 47 years). Complications (patients per year) after implantation were as follows: stenosis, 15%; sepsis, 4%; brain accidents, 4%; and reoperation, 7% in the former group. In the latter group, the results were 2%, 0, 2%, and 2%, respectively. Therefore, it is clear that in children there is a quicker and higher incidence of valve degeneration or stiffness leading to stenosis. Consequently, I believe the mechanical valve is superior to the xenograft in children.

DR. GERALD RAINER (Denver, CO): I, too, enjoyed not only the content of the paper of Dr. Williams, but the method in which it was presented. I want to comment on a smaller series of tissue valves in our hands over a period of five and a half years.

At the present time, we have been pleased with the performance of tissue valves. Until the end of November, 1979, 202 tissue valves had been used on our service—117 mitral, 72 aortic, and 13 tricuspid. Of these valves, 89 are Hancocks and they were all used early on, so that the ones we have been following the longest are a Hancock porcine series. Essentially all of the 55 Ionescu-Shiley valves used are in the aortic position, and 58 Carpentier-Edwards porcine valves were used. At the present time, our operative mortality has been 3.3% for those patients who are not undergoing multiple-valve replacement, who are not undergoing a second operation, and who are not over the age of 60 years.

Eight months after tissue valve replacement, 1 of our patients sustained a streptococcal septicemia, and although she was treated very promptly, there was considerable thickening of the valve secondary to the infection. This example illustrates the lack of ability of a tissue valve to withstand infection, especially *Streptococcus viridans*. The valve was replaced with a nontissue valve.

However, we had a chance to look at a valve that had been in for almost three and a half years and was perfectly pliable. Another valve was recovered after two years. Both of the patients had died of causes not related to the valve. The valve was subjected to a total analysis, including tensile strength, Hooke's modulus, and other routine examinations, and none of these showed any significant deterioration in the tissue so far as we could determine.

Our choice for valve replacement at the present time is the tissue valve in all positions and will continue to be until we have seen some reason to change. At the present time, out of the 202 valves, we have seen a single case of thromboembolism. This was in our fourth case of a mitral valve replacement. The mitral valves are anticoagulated on the basis of atrial fibrillation, giant left atrium, or a previous thrombosis. The aortic valves are not anticoagulated after an initial 6-week period.

DR. WILLIAMS. I appreciate the kind comments of the discussants and will reply to their questions in the order in which they were asked. Dr. Cohn, it appears in our series of patients that we use the Björk-Shiley prosthesis in approximately 75% of valve replacements and tissue valves in approximately 25%.

We have noted in our study no difference in the incidence of paravalvular leak or thromboembolism associated with any particular suture technique.

Our indications for the use of tissue valves may be best defined by telling you our indications as well as our relative contraindications. We believe tissue valves should be given strong consideration when the age of the patient will likely preclude a second operation, when the patient is in sinus rhythm, when there is any medical contraindication to anticoagulants, when any socioeconomic factors preclude compliance with a regimen of anticoagulants, and occasionally when a patient might desire to have a bioprosthesis in place. Situations in which less consideration is given to the use of tissue valves are those patients in chronic atrial fibrillation and those patients in whom anticoagulants are indicated because of any atrial anatomical problems or prior thromboembolism. For the most part, we are hesitant to use the porcine bioprosthesis in children and young adults. I will temper these remarks by saying the choice of a porcine bioprosthesis or prosthesis must certainly be individualized in every instance.

In reply to your last question, Dr. Cohn, we see no advantage to using a tissue valve in the presence of infection.

In reply to Dr. Wada, we basically agree with his comments and appreciate them. I thank Dr. Rainer for his kind comments.

Spontaneous Degeneration of Porcine Bioprosthetic Valves

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Fernando M. Jara, M.D., Min W. Lee, M.D., Mohsin Alam, M.D.,
Jeanne M. Riddle, Ph.D., and Paul D. Stein, M.D.

ABSTRACT **From October, 1971, to October, 1979, 490 patients with 560 porcine bioprosthetic valves were discharged from the hospital. During these 8 years, 23 valves were removed because of failure due to spontaneous degeneration. Bioprosthetic valve survival without degeneration was at 4 years, 98.9% ± 0.6 (standard error); at 5 years, 96.4% ± 1.3; at 6 years, 90.8% ± 2.4; and at 7 years, 84.2% ± 3.7. There was no difference in degeneration observed with regard to sex, valve position, or whether the valves were rinsed with antibiotics prior to implantation. There was an increase in degeneration in patients 35 years old and younger compared with those more than 35 years old ($p = 0.0001$). Valve failure was gradual, and valve changes were noted by echocardiogram and phonocardiogram prior to actual failure. Specific factors leading to degeneration require further investigation.**

In the 8 years from October, 1971, through October, 1979, 490 patients were discharged from the hospital after implantation of a porcine bioprosthetic valve. The 560 valves implanted in these 490 patients were considered "at risk" for failure. During these 8 years, 23 valves were removed for failure due to spontaneous degeneration. Here we review our experience with degeneration of the porcine bioprosthetic valve.

Materials and Methods

The descriptive terminology is that suggested by the committee formed to standardize nomenclature at the Symposium on Bioprosthetic Cardiac Valves in Munich, 1979, and known as the "Munich Terminology" [18]. The term *porcine xenograft* is therefore replaced by the more correct *porcine bioprosthesis*.

Patients were considered to have spontaneous degeneration of the porcine bioprosthesis if they were seen with valve incompetence or stenosis and if degenerative changes were confirmed on gross and histological examination of the explanted valve. In addition, there could not be any clinical, bacteriological, or histological evidence of infection. Twenty-three valves satisfied these criteria. All valves were manufactured by Hancock Laboratories.

Follow-up was conducted by personal examination, letter, or telephone interview with the patient, family, or physician. Of the 490 patients, all but 8 were accounted for in the year 1979. These 8 patients with 9 valves represent 341 months of valve follow-up lost to the study if based on an end point of October, 1979. Follow-up was therefore 98.3% complete.

Actuarial curves for valve survival without degeneration were constructed according to the method of Berkson and Gage [3]. Confidence limits were determined by the method described by Irwin [14]. Comparison between groups was determined by the chi-square test with matrix inversion. Comparison between groups with greater than one degree of freedom was made using Breslow's proportional hazards model [4].

Results

Valve survival without degeneration is depicted actuarially in Figure 1. The earliest degenerated valve was seen at 14 months. There were then no further instances of degeneration until the fortieth month. The percentage of valve survival without degeneration was as follows: at 4 years, 98.9% ± 0.6 (standard error); at 5 years, 96.4% ± 1.3; at 6 years, 90.8% ± 2.4;

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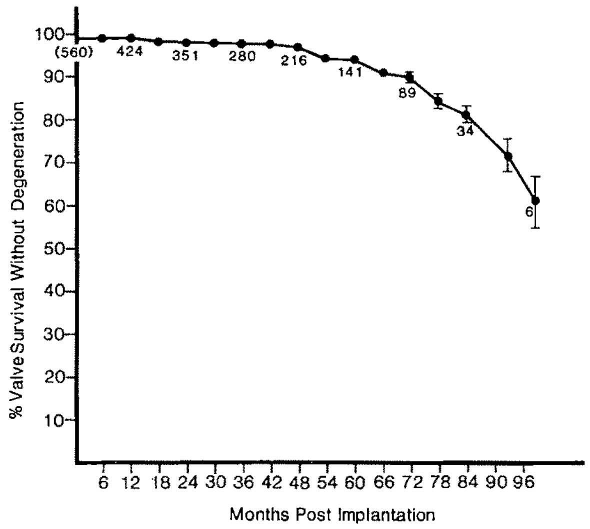


Fig 1. Percent survival without degeneration of porcine bioprostheses followed up to 96 months. Vertical lines denote standard error and numbers denote the valves at risk entering that particular period.

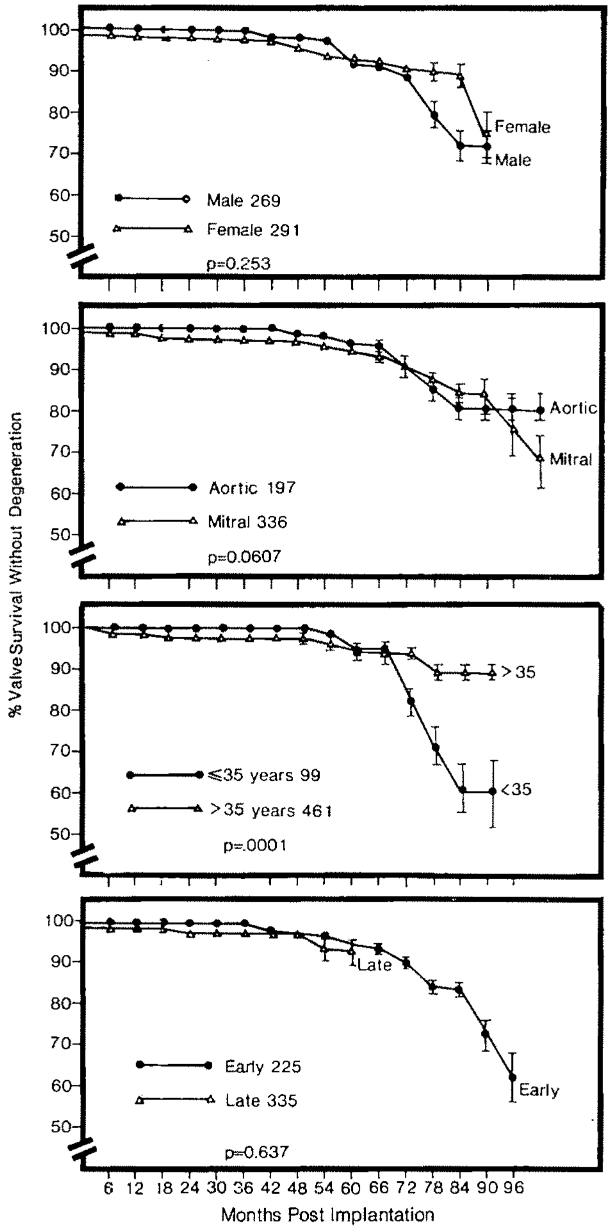


Fig 2. Actuarial survival of valves without degeneration for male and female patients, for the aortic and mitral position, for patients 35 years old and younger and for patients older than 35 years, and for antibiotic-rinsed valves (Early) *and non-antibiotic-rinsed valves* (Late). *The only significant difference was in patients 35 years and younger compared with those older than 35 years* (p = *0.0001).*

and at 7 years, 84.2% ± 3.7. At 8 years' follow-up there are only 6 valves remaining, and the percentage of survival without degeneration of 63.1% ± 11.7 is of questionable significance (70% confidence limits = 51.4% to 74.8%).

There were 269 valves in male patients and 291 in female patients. The survival of valves without degeneration is plotted actuarially in Figure 2. There is no significant difference between male and female patients with respect to degeneration ($p = 0.253$).

There were 197 aortic, 336 mitral, and 27 tricuspid valves at risk. Valve survival without degeneration is plotted actuarially in Figure 2. There is no significant difference in degeneration between valves in the aortic and mitral position ($p = 0.607$).

Survival without degeneration is plotted actuarially in Figure 3 for five age groups: 0 to 20 years, 21 to 25 years, 26 to 30 years, 31 to 35 years, and older than 35 years. Degeneration occurred with similar frequency in all age groups less than 35 years old. This is also shown in the Table using Breslow's proportional hazards model, and there is no significant difference in observed degeneration compared with the expected for any age group less than 35 years old. However the difference between all the groups less than 35 years old and greater than 35 years old is significant ($p = 0.0001$) and is displayed actuarially in Figure 2.

Prior to October, 1974, the porcine bioprosthetic valves were immersed in a solution containing 1 gm neomycin and 10,000 units of bacitracin in 100 ml of saline solution as outlined in the manufacturer's instructions [10].

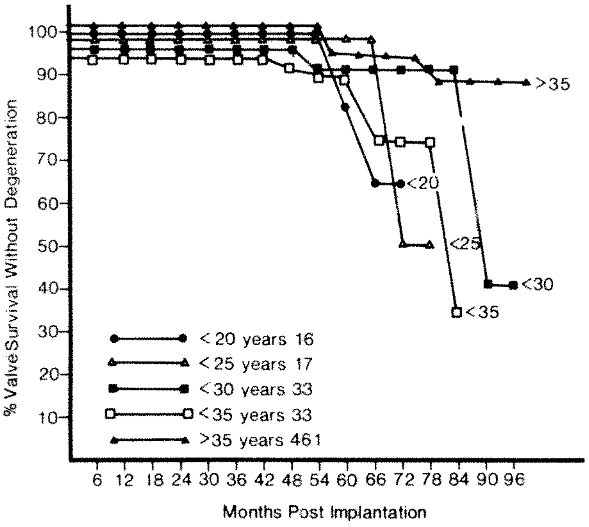


Fig 3. Actuarial survival without degeneration for porcine bioprostheses implanted in different age groups. The similar difference in all groups 35 years old and younger compared with those more than 35 years old is shown. The fact that not all groups had patients followed for the entire 96 months accounts for the different end points of the five curves.

This storage and handling information was revised October 1, 1974, with the warning that neomycin and bacitracin "will cause a chemical change tending to make the leaflets stiff" [11]. Subsequently, in our institution valves were rinsed only in lactated Ringer's solution. To determine whether antibiotic rinsing might play a part in degeneration, valves at risk implanted prior to October 15, 1974 (designated "early"), were plotted against those implanted subsequently and that did not undergo antibiotic rinsing. These latter valves were designated "late" (see Figure 2).

At 5 years, the percent surviving without degeneration was 97% ± 1.3 for the early group and 93% ± 6.0 for the late group. This is not a significant difference ($p = 0.6370$). However, as can be seen from the curves in Figure 2, if there is a difference between the early and late groups, it will not become evident until the sixth and seventh year of follow-up when the percent surviving without degeneration falls more sharply.

Clinical Features

Twenty of the 23 degenerated valves were removed at our institution. Of these 20 valves in 19 patients, the time between the onset of marked worsening of symptoms and reoperation ranged from zero to 12 months and averaged 3.7 months. The 1 patient with no symptoms was noted to have a major aortic prosthetic incompetence murmur on routine follow-up. Although he was asymptomatic, valve replacement was carried out because of 4+ valvular incompetence and increasing left ventricular size and elevation of the left ventricular end-diastolic pressure.

Cardiac catheterization was carried out in 18 of the 19 patients seen in our institution. All aortic valves showed 4+ incompetence, and 1 of the 6 showed a peak systolic gradient of 88 mm Hg across a 27 mm valve. All mitral bioprostheses showed 4+ incompetence and of the 12 valves studied, 8 showed mean diastolic gradients greater than 5 mm Hg. The gradients did not appear to be related to the valve size because 7 of the 8 valves with substantial gradients were 31 or 33 mm. The only tricuspid valve was not incompetent but had a 9 mm mean diastolic gradient. Two patients, 1 with porcine aortic and mitral valves and 1 with porcine aortic, mitral, and tricuspid valves, had continued excellent function of their aortic bioprosthesis while the other valves (mitral, and mitral and tricuspid) were removed because of degeneration.

Among the 19 patients operated on in our in-

Porcine Bioprosthesis Degeneration by Age Group

	Age (yr)				
Variable	0–20	21–25	26–30	31–35	> 35
Valves at risk	16	17	33	33	461
Degeneration observed	3	1	4	3	12
Degeneration expected	0.6	0.3	2.3	0.8	19.0

stitution, there was 1 hospital death. This occurred in the late postoperative period and was due to the formation of a subannular aneurysm in a 50-year-old woman who had undergone her fourth mitral valve operation.

Seven degenerated porcine valves were replaced with Björk-Shiley valves and 13 with a new porcine bioprosthesis. The choice of a second porcine bioprosthesis was most often the patient's and was based on a desire to avoid anticoagulation.

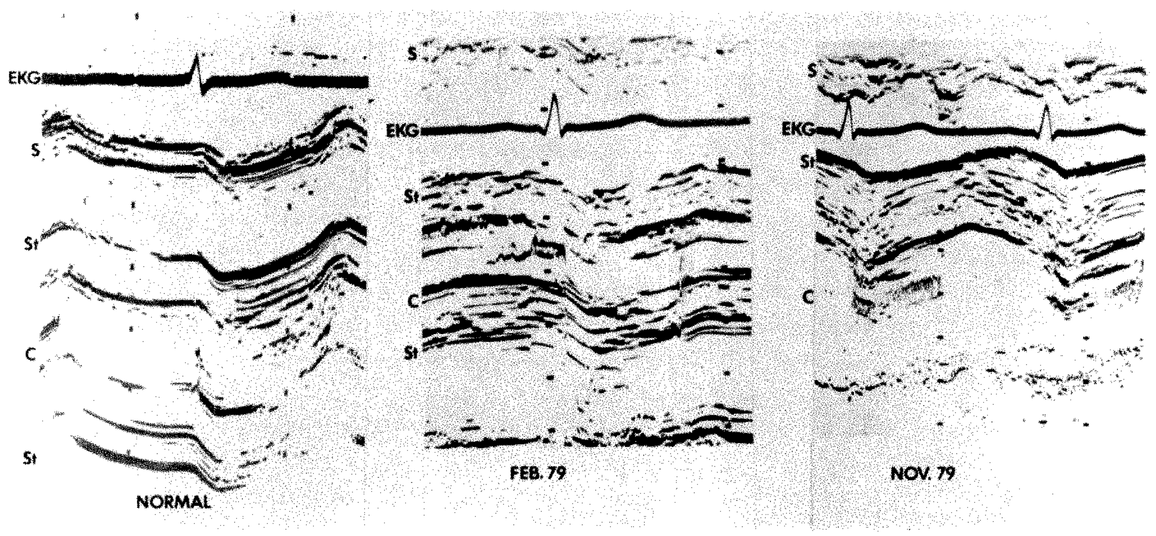
Echocardiography

The echocardiographic features of the degenerated porcine bioprosthesis have been reported from this institution [1a]. When this experience with the degenerated valve is combined with the experience of serial echocardiographic analysis of bioprosthetic valves that have not degenerated, a pattern of progressive cusp thickening can be seen [1]. The mean thickness of valve cusps in the coapted position was appreciably greater in valves studied 48 months after operation compared with valves studied within 2 months of implantation. A thickness of more than 3 mm had a high correlation with severe valve dysfunction. Echocardiographic progression from thickening to cusp rupture over a 9-month period is shown in Figure 4, documenting the value of this method of following patients with porcine bioprosthetic valves.

Phonocardiography

The frequency spectrum of the aortic component of the second sound (A_2) has been studied in 44 patients with aortic bioprostheses [22]. In 12 patients with porcine valves implanted for 18 months or less, the A_2 did not differ substantially from that in patients with normal natural aortic valves. However, in 19 patients with porcine valves implanted 5 to 7.5 years previously, the dominant frequency of A_2 was higher and in the range of that observed in patients with aortic stenosis (Fig 5). Two of the patients in this latter group required replacement for incompetence due to porcine valve degeneration. Similar progression to higher frequency of the first heart sound has been found in porcine valves implanted in the mitral position for longer than 4 years. Analysis of the frequency spectrum of heart sounds appears to be a valuable tool in detecting degeneration of porcine bioprosthetic valves.

Fig 4. Echocardiograms of a porcine bioprosthesis in the mitral position. (Left) A normally functioning bioprosthesis with a thin cusp (C) *in the closed position. (Center) Echocardiogram from a patient seen in February, 1979, with cusp thickening in the closed position of greater than 3 mm. At this time, the patient had no murmur and no symptoms. (Right) Nine months later, in November, 1979, the echocardiogram in this same patient showed a flail cusp, noted by the fluttering of the cusp tracing. At this time, the patient had major symptoms and underwent successful prosthesis replacement.* (EKG = *electrocardiogram;* S = *septum;* ST = *stent.)*



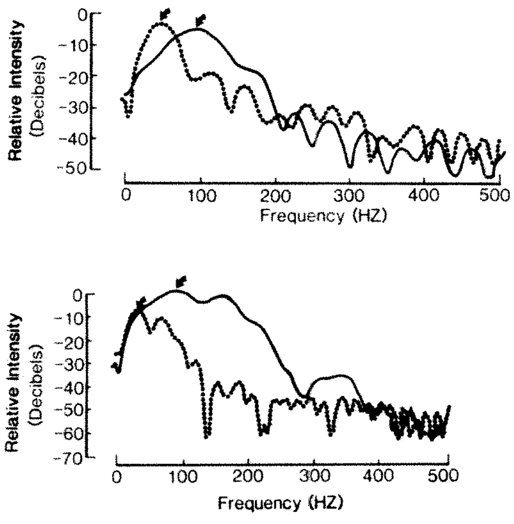


Fig 5. (A) Frequency spectrum of the aortic component of the second sound in a patient with a normal aortic valve (dotted line) *and a patient with calcific aortic stenosis* (solid line). *(B) Frequency spectrum of the aortic component of the second sound in a patient with a porcine bioprosthesis implanted for three days* (dotted line) *and another in a patient whose porcine bioprosthesis had been implanted for 6 years* (solid line). *The dominant frequency is shown with an arrow. (Adapted from Stein et al [22].)*

Pathology

Gross pathology of the explanted bioprosthetic valves ranged from simple tears of cusps to marked calcification and cusp destruction. In describing histological changes, the terminology of Gross and Kugel [9] was used: inflow endocardium, ventricularis, spongiosa, fibrosa, outflow endocardium, and aorta. Calcification was found in all layers including the aorta and occasionally replaced the full thickness of the valve leaflet. When linear calcification occurred in the ventricularis and fibrosa, there was often transverse tearing of the leaflet. Longitudinal tearing was common when the calcification was heavy along the outflow endocardium. Less calcified valves often displayed palisading of mononuclear cells with occasional multinucleated giant cells and fibrin along the surface of the outflow endocardium and of the inflow endocardium to a lesser extent. There did not appear to be any correlation between the severity of the degeneration and the duration of implantation. However, the degenerated valves of younger patients tended to be more heavily calcified. These findings will be reported separately.

Surface Morphology

Eight porcine bioprosthetic valves were examined using the scanning electron microscope. Six had been implanted from 41 to 83 months, and 2 were examined directly from the manufacturer to determine the surface morphology of the unimplanted porcine bioprosthetic valve [19a].

The majority of the surface of the outflow endocardium and to a lesser extent of the inflow endocardium of the unimplanted valves demonstrated the fibrous appearance of exposed subendocardium (Fig 6A). There was a substantial difference in the degree of exposed subendocardium of the 2 unimplanted valves, which probably reflects a difference in processing or in the degree of autolysis prior to processing. Loss of endocardium was more marked in the degenerated valves. Some areas were covered by a smooth layer of material, presumably basement membrane, interrupted by numerous patches of exposed fibers of subendocardium. Activated leukocytes were attached to the subendocardial layer as well as single platelets and platelet aggregates of both dendritic (reversible) and spread (irreversible) type (Fig 6B). The adherent platelets showed a considerable degree of surface activation as evidenced by pseudopod extrusion. Studies using ex vivo techniques [20] have shown that this platelet surface activation is widespread throughout the patient's circulating platelet population prior to removal of the degenerated valve.

Comment

Spontaneous degeneration of the porcine bioprosthetic valve has been reported to occur in isolated instances [5, 13] or sporadically in large series [6, 7, 19]. The previously reported experience of our institution [17] is updated by this report. Currently, the incidence of degeneration is 3.6% at 5 years, 9.2% at 6 years, and 15.8% at 7 years. The incidence of degeneration does not appear to be related to sex or valve position. The lack of difference in degeneration between the aortic and mitral position differs somewhat from another report from our institution [16]. The difference can be attributed to the exclusion of infection-related failure in

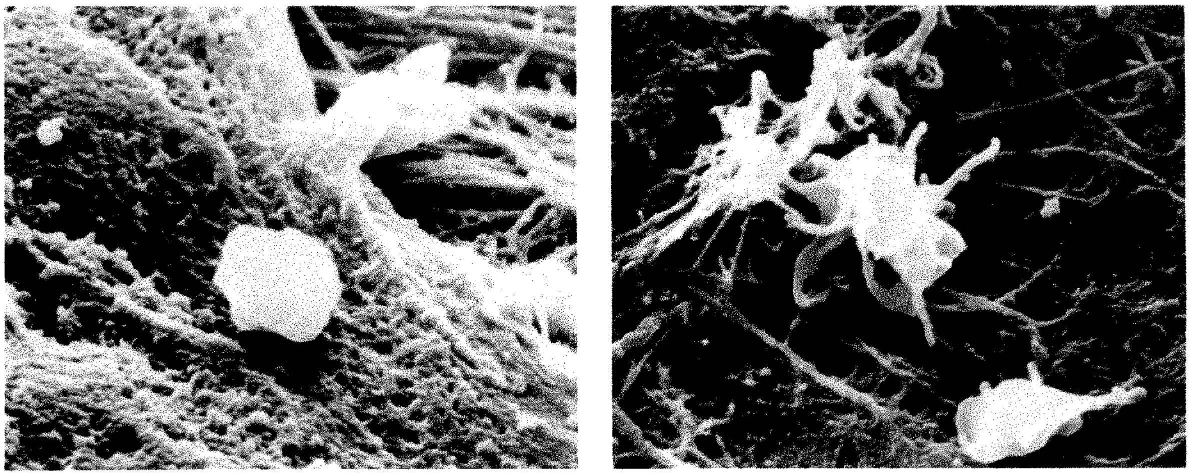


Fig 6. (A) Scanning electron microscopic view of a degenerated porcine bioprosthesis showing loss of endocardium and exposure of subendocardial collagen. (B) Adhering platelets show formation of dendrites and spreading of hyalomeres. These features reflect surface activation. (A: ×550 before 40% reduction; B: ×7,700 before 40% reduction.)

the present report and the inclusion of a larger number of valves at risk (560 versus 190) followed for a longer period of time. Antibiotic rinsing of the valves prior to implantation did not appear to influence the incidence of degeneration compared with non-antibiotic-rinsed valves at 5 years' follow-up. Like others [2, 15], we found an increased incidence of degeneration in younger patients. However, analysis of age groups suggests that degeneration occurs earlier in patients up to the age of 35 years and not just in children.

Valve failure was almost always associated with a gradual worsening of symptoms. Although the change in symptomatology might be abrupt and require reoperation within a month, there was no catastrophic failure as has been associated with mechanical valves. This gradual change contributed to the low mortality associated with reoperation. We are encouraged that besides the clinical examination, echocardiography and phonocardiography can be used to detect structural changes in the valve prior to the onset of a new murmur. In the fifth year after implantation, these techniques as well as frequent clinical examinations should be helpful in detecting valve failure. The gross and microscopic pathological involvement in our explanted degenerated valves did not differ from that of previously reported series [8, 12, 21]. However, the extent of denudation of endocardium with activated platelets and leukocytes on the exposed collagen and the activation of the patient's circulating platelet population offer the opportunity for intriguing speculation into the pathogenesis of degeneration. The morphology of platelets on the valve reveals these platelets are active and interacting with the porcine tissue. The platelet products released from these aggregates may trigger the circulating population of platelets, thereby causing further aggregation. The resulting platelet and fibrin thrombi may lead to cusp thickening and surface calcification. The activated leukocytes on the cusp surface may signal the breakdown of collagen through the release of lysosomal enzymes such as collagenase, or may signal an immunological event [19a]. Still unexplained is the calcification occurring in the spongiosa.

We continue to use the porcine bioprosthesis as the primary cardiac valve prosthesis. We are aware of an incidence of spontaneous degeneration of 9% at 6 years but believe that valve degeneration can be monitored well clinically and, in fact, be predicted echocardiographically and perhaps by frequency spectrum analysis of heart sounds. Since valve failure is gradual and not catastrophic, reoperation can be accomplished safely. The surface changes in the valves and activation of the patient's platelet population suggest that degeneration might be modified by agents that decrease the attraction of formed elements of the blood for exposed collagen. However, specific factors leading to degeneration in younger patients as well as additional causes for sporadic failure of glutaraldehyde-treated porcine valves require further investigation.

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Discussion

DR. JURO WADA (Tokyo, Japan): The disadvantages of the Hancock valve are the broad sewing ring, which makes the external to internal diameter ratio suboptimal, and the cusp with limited mobility, which compromises central flow, especially in small-sized valves. Dr. E. Imamura and I have designed a porcine valve that has a central opening when it is processed with glutaraldehyde. This makes the valve cusps more mobile, especially in a low pressure chamber in our laboratory. We are hoping that this type of xenograft valve with its better leaflet mobility will delay the so-called spontaneous degeneration process. I wonder if the authors have found that some cusps show more degeneration than others.

DR. CHARLES L. MC INTOSH (Bethesda, MD): I compliment Dr. Magilligan on this very thorough reporting of his experience at the Henry Ford Hospital concerning spontaneous degeneration of the Hancock porcine bioprosthesis. At the National Institutes of Health, the clinical experience with the Hancock valve is now nearing 10 years, with 491 valves implanted in 372 patients since July, 1970. Sixty-nine patients have survived operation for more than 4½ years, and, in this group of 69 patients, we have seen 10 valves degenerate in 8 patients (8 mitral and 2 tricuspid valves). Degeneration occurred at 56 to 104 months, with the average being 77.3 months following implantation.

In our series, the usual forms of dysfunction resulted from leaflet disruption secondary to collagen degeneration, calcification, and thrombosis of the prosthesis. For the sake of discussion, I mention another mechanism, that of a physical change in the flexible stent resulting in the ultimate dysfunction of the valve. Two bioprostheses explanted at the time of operation (75 and 104 months) and 1 removed postmortem (93 months) showed marked inward flexion of the three struts—the "creep" phenomenon. Whatever advantage is provided by the flexible stent is decreased or lost when creep occurs because of the change in stress forces on the porcine valve. Severe mitral stenosis was found at catheterization in the patient operated on at 104 months. At operation, a morphologically normal valve, except for a small pinhole in one leaflet, was found. The stenosis was secondary to marked creep of the struts, which caused obstruction of the secondary valve orifice.

Several mechanisms for the creep phenomenon can be postulated: (1) oversizing the prosthesis relative to the annulus or ventricular size, resulting in inward flexion at the time of operation; (2) loss of flex life of the polypropylene as a function of time; and (3) manufacturing changes in stent thickness or tension on the stent caused by the applied cloth covering. Therefore the creep phenomenon observed can produce ultimate dysfunction or appreciable hemodynamic stenosis of the bioprosthesis. I hope that this phenomenon will be prevented in future by engineering changes in the material, stent thickness, or stent design.

DR. MAGILLIGAN: I thank Dr. Wada for his comments. In reply to his question, we have not seen any particular cusp undergo degeneration more frequently than another.

I appreciate Dr. McIntosh's comments because our experience is quite similar with regard to degeneration. We have not seen polypropylene stent creep except in 1 patient in whom a 60 mm gradient developed in the aortic position. We thought this was responsible for his hemolytic anemia and reported it separately but did not include it under valve degeneration.

I agree with Dr. McIntosh that the bioprosthetic valve remains the valve of choice. Failure is gradual and not catastrophic, and reoperation can be accomplished safely. I prefer to deal with degeneration rather than thromboembolic stroke, bleeding because of anticoagulants, or valve thrombosis. I urge that all surgeons know the prosthesis they choose, be aware of its problems, and be ready to deal with them.

Cardiac Operation and End-Stage Renal Disease

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Gary Francis, M.D., Christina M. Comty, M.D., and Hovald K. Helseth, M.D.

ABSTRACT **From 1972 to 1979, 22 patients with end-stage renal disease underwent 23 cardiac operations involving the pump oxygenator. Fourteen patients had coronary artery bypass, 2 had aortic valve replacement, 2 had mitral valve replacement (MVR), 2 had MVR with coronary artery bypass, and 2 had ascending aortic root replacement with a composite graft. One patient underwent successful reoperation for a false aneurysm of the left ventricle after MVR. There were 2 postoperative deaths, for a mortality of 9.1%. The patients undergoing coronary artery bypass had an average of 2.7 grafts and an average Functional Class improvement from New York Heart Association Class III or IV to Class I or II. Eighteen patients required preoperative and postoperative dialysis to control blood volume, potassium, and uremia. Four patients had functioning renal transplants, and 4 patients underwent subsequent successful renal transplantation. We conclude that: (1) patients who have transplants and require dialysis can be successfully managed for cardiac operation in spite of their complex associated medical problems; (2) functional and symptomatic improvement simplifies continued management of the patient needing dialysis; and (3) improvement of a cardiac disability can allow favorable renal transplantation in selected patients.**

Cardiac surgical problems in patients with end-stage renal disease are occurring more frequently because of a growing number of patients at risk. There were 37,000 dialysis patients registered for Medicare coverage for end-stage renal disease on December 31, 1978. This includes approximately 95% of all patients on long-term dialysis in the United States. Fifty-nine thousand are projected for 1980. Uremic pericarditis, bacterial endocarditis, and atherosclerotic coronary artery disease account for most cardiac surgical problems.

In general, the problems of uremic pericarditis have been controlled with intensified dialysis, corticosteroids, and anti-inflammatory drugs. Pericardiectomy for constriction or tamponade is effective when conservative means have failed [6, 12, 15]. Endocarditis is associated with arteriovenous fistulas and cannulas whether they are infected or noninfected. Antibiotic treatment alone for endocarditis has been ineffective in patients requiring dialysis [10, 14, 17], whereas several instances of antibiotic treatment in combination with valve replacement have been successful [7, 11, 23].

Coronary artery disease looms as a larger problem due to accelerated atherosclerosis in the dialysis patient, and 50% of deaths in these patients are associated with atherosclerotic complications [18]. This appears to be related to hypertension, hypercalcemia, and hyperlipidemia, all of which have an elevated incidence in dialysis patients [1, 9, 18, 24]. The effectiveness of dialysis is limited when angina or hypotension occurs during dialysis, and volume overload may become a problem [16]. Patients at risk with unstable coronary artery disease may also be restricted from renal transplantation. On the other hand, transplantation may not reverse the trend of accelerated atherosclerosis [3].

Surgical treatment of the complications of bacterial endocarditis and coronary artery disease requiring cardiopulmonary bypass can be accomplished in patients with end-stage renal disease with acceptable results [2, 4, 5, 7, 8, 13, 20–22]. Functional and symptomatic improvement result, thereby simplifying dialysis management and increasing chances for renal transplantation [19].

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Material

From February 18, 1972, to January, 1980, 23 cardiac operations requiring cardiopulmonary bypass were performed on 22 consecutive patients with end-stage renal disease from the Hennepin County Medical Center and its Regional Kidney Disease Program. These surgical procedures were as follows: coronary artery bypass, 14 patients; coronary artery bypass with mitral valve replacement (MVR), 2; aortic valve replacement (AVR) for endocarditis, 2; MVR for endocarditis, 1; MVR for rheumatic mitral stenosis, 1; composite graft, 2; and repair of left ventricular false aneurysm, 1.

At the time of writing, there were 330 patients with long-term dialysis in the Regional Kidney Disease Program. The surgical patients ranged from 38 to 73 years old (average age, 54.7 years). Fourteen patients required long-term hemodialysis and 1, long-term peritoneal dialysis. Two had short-term dialysis for renal failure secondary to acute cardiac decompensation. One patient began long-term dialysis two months after coronary artery bypass. His sole remaining kidney with hypernephroma was removed as part of a staged approach to severe angina and renal malignancy. Four patients had functioning renal transplants at the time of operation. The duration of long-term dialysis before operation averaged 28 months (range, 1 to 144 months). Three of 4 patients with functioning renal transplants had previously had dialysis for periods of 3 to 38 months.

The etiology of renal failure varied. Nine patients had renal failure due to glomerulonephritis, 2 patients had polycystic kidneys, and 3 had hypertensive arteriolar nephrosclerosis. There was 1 patient each with milk-alkali nephrocalcinosis, diabetic glomerulosclerosis, and cardiogenic shock secondary to myocardial infarction imposed on chronic renal insufficiency. Two had acute tubular necrosis due to acute ascending aortic dissection. One patient had bilateral nephrectomy for hypernephroma. The etiology in 2 was undetermined. Most patients had multiple associated problems, with hypertension, secondary hyperparathyroidism, hyperlipidemia, and peripheral vascular disease being the most common (Table 1).

Table 1. Associated Diseases in Patients with End-Stage Renal Disease

Disease	No. of Patients (N = 22)
Hypertension	14
Secondary hyperparathyroidism	7
Hyperlipidemia	4
Atherosclerotic peripheral vascular disease	3
Hepatitis virus A	2
Previous uremic pericarditis	2
Previous pancreatitis	2
Peptic ulcer disease	2
Renal lithiasis	2
Gout	2
Chronic obstructive pulmonary disease	2
Paroxysmal atrial tachycardia	2
Diabetes mellitus	2
Diabetic retinopathy and blindness	1
Atherosclerotic cerebral vascular disease	1
Hypothyroidism	1
Esophagitis	1
Alcoholism	1

Sixteen patients had symptomatic atherosclerotic coronary artery disease, and 2 of these had substantial mitral regurgitation requiring MVR. Preoperatively, 11 were in New York Heart Association (NYHA) Functional Class IV and 5 in Class III. Three had normal left ventricular end-diastolic pressures at rest, and none had normal pressures with exercise or following ventriculography. All ventriculograms were abnormal, ranging evenly from poor to good (Table 2). Fourteen patients underwent coronary artery bypass alone. Per patient, there was an average of 2.8 vessels involved with stenosis of 75% or greater. All workable diseased vessels were bypassed, for an average of 2.7 grafts per patient.

Two patients with triple-vessel disease and substantial mitral regurgitation underwent coronary artery bypass and MVR with porcine valves. One of these patients had antegrade

Table 2. Results of Left Ventriculography in 16 Patients with Coronary Artery Disease and End-Stage Renal Disease

Variable	Result
WALL MOTION	
Normal	0
Good	6
Fair	6
Poor	4
Total	16
MITRAL REGURGITATION	
1+	2
2+	1
3+	2
Total	5

MVR through the left atrium with two vessels bypassed. The other had retrograde valve replacement through a posterior scar and a single vessel bypassed. These patients were in Functional Class III and IV, respectively.

Three patients with bacterial endocarditis required valve replacement; 2 had AVR and 1, MVR. The infections were caused by *Staphylococcus albus, Staphylococcus epidermidis,* and enterococcus. All 3 patients had arteriovenous shunt infections. Two of these patients were in Functional Class II and the third in Class IV.

One patient had MVR for rheumatic mitral stenosis. Preoperatively the patient was in Functional Class III with pulmonary hypertension.

Two patients had acute dissections of the ascending aorta with hemopericardium and were in acute renal failure at the time of diagnosis. They underwent aortic root replacement with a composite graft utilizing a No. 27 Björk-Shiley valve in a 30 mm woven Dacron tube graft. The coronary ostia were reimplanted into the graft. Both patients were critically ill preoperatively. Despite acute renal failure, both underwent operation prior to institution of short-term hemodialysis.

Management

Special attention must be paid to the problems of intravascular volume, potassium balance, anemia, and drug administration in patients requiring dialysis. Preoperatively, patients were given shortened daily dialysis runs against a low potassium bath to control serum and total-body potassium. Hematocrits were raised to 30% by transfusing packed cells during dialysis. The patients were sent to operation at dry weight. During operation, intravenously administered fluids were kept to a minimum and no potassium was given. A prime of blood and Ringer's lactate solution was used in the pump to prevent excessive hemodilution. Volume loading from the pump off bypass was kept to a minimum, as judged by blood pressure and cardiac output. The freshest available blood was used for replacement. Consequently, hyperkalemia was not a problem and volume overload occurred in only 1 patient. Postoperative dialysis was generally not necessary until the second or third postoperative day. The need for dialysis was based on the level of potassium and blood urea nitrogen and the volume balance of the patient. Careful regional heparinization was used during postoperative dialysis for approximately seven to ten days. Drug dosages were reduced to recommended levels for anephric patients. Perioperative antibiotics, either cephalothin or cefazolin, were used.

Patients with a functioning transplant were managed routinely. Care was taken to give adequate adrenocortical support and to maintain urine output.

Results

There were 2 operative deaths among the 22 patients, for an overall mortality of 9.1%. These deaths occurred in the 2 patients who had coronary artery bypass. One death was due to sepsis beginning as a pseudomonas leg wound infection. The second death was in a patient with severe triple-vessel disease in whom fibrillation occurred upon induction of anesthesia. His operation was completed but he was unable to come off bypass because of poor cardiac output and intractable ventricular arrhythmias.

Table 3. Intraoperative and Postoperative Complications in 17 out of 22 Patients with End-Stage Renal Disease

Complication	No. of Patients
Pericarditis	4
Atrial arrhythmia	3
Dialysis-related mental changes	3
Postoperative bleeding	2
Perioperative myocardial infarction	2
Prolonged respiratory support	2
Pneumonia	2
Cytomegalovirus pneumonitis	1
Sternal wound infection	1
Leg wound infection	1
Pulmonary edema	1
Ketoacidosis	1
Left ventricular false aneurysm	1
Digitalis toxicity	1
Pleural effusion requiring drainage	1
Pneumothorax	1
Gastrointestinal bleeding	1
Splenic abscess	1
Spontaneous splenic rupture	1
Acute brain syndrome	1
Total	31

Seventeen patients had 31 complications, for a complication rate of 77.3% (Table 3). Bleeding problems were not directly related to dialysis. Intraoperative bleeding was a problem with 1 patient who had aortic dissection and 1 who had AVR. Two patients were reexplored for bleeding. One patient had intraabdominal hemorrhage from a spontaneously ruptured spleen, which was removed.

Infections were increased, and 1 patient, as noted, died of wound sepsis. One sternal wound infection occurred. Two patients had bacterial pneumonia, and 1 patient with a transplant had cytomegalovirus pneumonitis. One patient with endocarditis had a splenic abscess postoperatively caused by the same organism that infected the valve.

Other problems related to renal failure were alterations in mental status secondary to dialysis in 3 patients and digitalis toxicity in 1 patient. Wound healing in patients with renal failure, especially the immunosuppressed transplant patients, was less secure. Careful attention to hemostasis and suturing technique is especially important. Buttressed mattress sutures were used during all valve replacements.

Follow-up has been obtained at a recent clinic visit or hospitalization, or by a personal telephone interview. The survivors have been followed from 4 to 81 months (mean, 32 months).

Two late deaths occurred, both among the patients who had valve replacement. One patient with endocarditis died of a myocardial infarction 14 months after AVR and 12 months after renal transplantation. The second patient died of a cerebral vascular accident 39 months after MVR for mitral stenosis.

The patients receiving coronary artery bypass alone have been followed from 4 to 55 months (average, 17.8 months). They are all in NYHA Functional Class I or II with the exception of 1 who is in Class III.

The 2 patients who had MVR and coronary artery bypass are both improved one Functional Class. In the patient receiving retrograde MVR, a left ventricular false aneurysm formed a month after operation. This patient recovered following reoperation.

The 2 late surviving patients who underwent valve replacement for endocarditis are in Functional Classes I and II at 49 months and 3 months, respectively. The 2 patients with composite grafts are in Functional Classes I and II at 75 and 81 months, respectively.

Three of 4 patients with functioning renal transplants at the time of operation are alive. Two of them have functioning transplants. Four patients have had renal transplantation subsequent to cardiac operation. Three of 4 are alive with functioning transplants.

Comment

From this study we drew the following conclusions:

1. Patients who require dialysis and who have renal transplants can undergo cardiac operation with an acceptably low mortality despite the associated medical problems.
2. Cardiac improvement simplifies management of the long-term dialysis patient and

permits other required operation as well as an opportunity for renal transplantation.

3. Multiple complications will occur, and a successful outcome requires a careful emphasis on surgical technique and close postoperative coordinated management.

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Discussion

DR. JOHN J. COLLINS JR. (Boston, MA): Dr. Monson and his group are to be congratulated for obtaining these excellent results in a very difficult group of patients. Patients with renal failure, of course, have multiple-system difficulties, including troubles with blood clotting and trouble resisting infection, and were not considered reasonable candidates for cardiopulmonary bypass, at least in its first years. Beginning about 1975, however, reports have been published indicating that this is not necessarily true, and this update by Dr. Monson and his group is very valuable.

I agree in general with their principles of management, but I do have a few points to make. First, the recommendation that dialysis be delayed for several days after operation has not been found necessary in our experience. In fact, at our institution, these patients are dialyzed on the day of and the day following operation. We use regional heparinization and have not noticed any problem with bleeding. I think the utilization of fresh-frozen plasma and platelet concentrates completely obviates difficulties with bleeding that are peculiar to patients with renal disease.

In recent years, we also have utilized a concentrated antibiotic program, that is, we use both a Keflin (cephalothin sodium)-type drug together with gentamicin, often a single dose of gentamicin, and discontinue all antibiotics after the fourth day. In patients with prosthetic devices, we continue to use a single dose of Keflin given intravenously about ten minutes prior to the beginning of dialysis. We continue that prophylactic bolus protection for about 3 months, at which time further antibiotics are discontinued. Perhaps Dr. Monson will comment on this type of program.

It is interesting that Dr. Monson did not mention any incidence of late endocarditis in patients on continuing dialysis. We, also, have not observed late endocarditis even in patients with prosthetic valves.

Like Dr. Monson's group, we discontinued the use of porcine valves in patients with end-stage renal disease. We observed two instances of premature calcification in a porcine bioprosthesis in such patients and consider these valves an unnecessary risk.

In patients with end-stage renal disease, we recently have begun to do routine pericardiectomy from phrenic nerve to phrenic nerve. It adds virtually nothing to the operation but might prevent some difficulties in the future.

DR. MONSON: We have not necessarily delayed the dialysis for fear of bleeding. It just hasn't been considered necessary on the first postoperative day. However, we have had no reluctance to use it on the first postoperative day and in general the last dialysis is within the 24 hours prior to operation.

We have not used any special antibiotic regimen other than Keflin prophylaxis, unless some other organism is known to be present in the patient preoperatively. When this has happened, the organism usually has been sensitive to gentamicin, and we have used a single bolus of this antibiotic, as Dr. Collins described.

We are aware of the problems with porcine valves and in general do not use them in the transplant and dialysis patient. However, the 2 patients in whom they were implanted were very ill and had a relatively short expected longevity. We thought that since the patients had both mitral valve disease and poor cardiac output, a porcine valve would offer some advantages with regard to thromboembolism.

We have not employed pericardiectomy but agree that it is a good idea and would not increase the risk of operation.

Notice from the American Board of Thoracic Surgery

The American Board of Thoracic Surgery will give a voluntary recertification examination in the fall of 1981. Diplomates interested in participating in this examination should maintain a documented list of their cardiothoracic operations performed two years prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings and other continuing medical education activities for the two years prior to application for recertification.

Some time during the summer, a Recertification Brochure will be mailed to all diplomates outlining the rules and requirements established for recertification in thoracic surgery. This brochure will also contain information about applying for the voluntary recertification examination.

Please address all communications to the American Board of Thoracic Surgery, 14640 E Seven Mile Rd, Detroit, MI 48205.

Improved Results in Newborns Undergoing Coarctation Repair

James Campbell, M.D., Raymond Delorenzi, M.S., John Brown, M.D.,
Donald Girod, M.D., Roger Hurwitz, M.D., Randall Caldwell, M.D.,
and Harold King, M.D.

ABSTRACT **Among 172 children who underwent repair of coarctation of the thoracic aorta from June 1, 1967, to June 1, 1979, there were 50 who were less than 6 weeks old. A review was undertaken to assess mortality and postoperative residual hypertension in this newborn age group.**

Forty-five (90%) had one or more associated congenital cardiac lesions, which were repaired or palliated at the time of coarctation repair. The three most common associated lesions were patent ductus arteriosus (74%), atrial septal defect (74%), and ventricular septal defect (62%). Thirty-one newborns underwent resection with primary end-to-end repair with 8 deaths (26%), and 18 underwent Dacron patch angioplasty and 1 underwent subclavian angioplasty with 4 deaths (21%).

Of the 38 survivors, 36 (95%) had good pedal pulses on postoperative clinical examination 3 months to eleven years postoperatively. Seventeen (45%) had upper and lower extremity blood pressure measured; 2 (5%) showed residual upper extremity hypertension (greater than 2 standard deviations above the mean and a gradient less than 20 mm Hg). One of these 2 patients has undergone repeat repair.

Based on this low mortality and infrequent need for repeat repair, we advocate aggressive early operation and judicious use of palliative procedures in newborns, when indicated, for associated defects.

Beginning with the reports of Gross [6] and Crafoord and Nylin [2], the results of surgical treatment of coarctation of the aorta have progressively improved. Today the outcome of such treatment in children and young adults is gratifying. The same has not been true for the infant age group. Of the 172 patients who underwent coarctation repair at the Indiana University Medical Center between June 1, 1967, and June 1, 1979, 12 of the 15 deaths occurred in patients less than 6 weeks old (Fig 1). The uniform presence of congestive heart failure and high incidence of associated congenital cardiac anomalies combined with the technical difficulty of operation and increased incidence of residual or recurrent coarctation make this age group unique and challenging. This report describes our experience with the surgical management and follow-up evaluation of 50 consecutive infants who were seen during the first 6 weeks of life.

Materials and Methods

Between June 1, 1967, and June 1, 1979, 172 children underwent repair of coarctation of the aorta at the Indiana University Medical Center. Of these, 50 patients were less than 6 weeks old at the time of operation. This young subgroup is considered in detail.

There were 36 male and 14 female infants with a mean age at operation of 2.56 weeks. The primary indication for operation in all patients was intractable cardiac failure. Forty-five patients (90%) were seen with one or more associated congenital cardiac anomalies.

All patients underwent preoperative cardiac catheterization, which included intracardiac pressure determinations, oximetry measurements, and aortography. The site of coarctation, the presence of aortic arch hypoplasia, and the nature of the associated cardiac defects were defined. All 45 patients with associated defects had at least one palliative or reparative procedure performed in addition to coarctation repair.

The postoperative follow-up period extended from 3 months to eleven years. Information was obtained by review of hospital and outpatient

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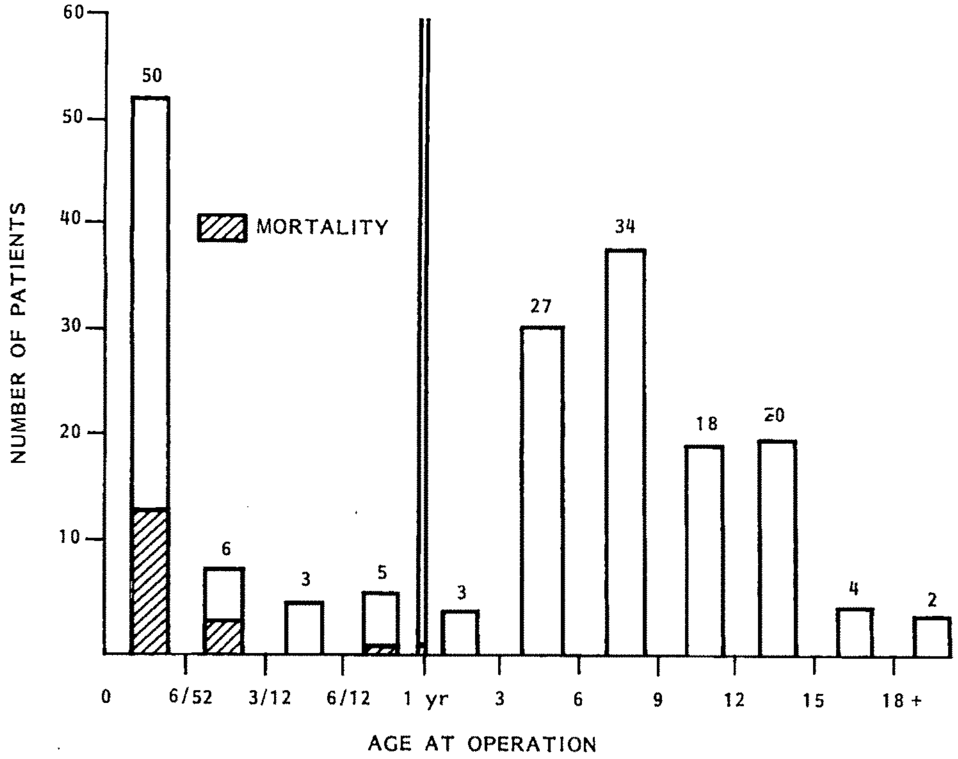

Fig 1. Age at operation of 172 patients who underwent repair of coarctation of the aorta at Indiana University during a twelve-year period.

records. Data consisted of systemic blood pressure evaluation, clinical examination, and comparison of upper and lower extremity pulses and blood pressure.

Operative Technique

Thirty-one patients (62%) underwent resection with end-to-end anastomosis, 18 patients (36%) underwent Dacron patch aortoplasty, and 1 patient (2%) was treated with subclavian patch angioplasty. There was no systematic assignment of patients to one group or another. Prior to 1978, resection with end-to-end anastomosis was the preferred procedure. Since that time, Dacron patch aortoplasty has been utilized nearly exclusively. We are attracted to this procedure because of its relative ease, the shorter operating time, the potential for growth of the remaining aortic wall, and recent reports such as that by Freed and co-workers [4] concerning the lowered postoperative exercise gradients in patients repaired using this technique.

All operations were performed through a left posterolateral thoracotomy. The pleural space is entered through the fourth intercostal space or the bed of the unresected fourth rib. Regardless of the proposed procedure, the distal transverse aortic arch, the left subclavian artery, the first two or three pairs of intercostal arteries, the ductus arteriosus, and the distal aorta are dissected free and controlled. If resection is to be performed, the involved segment must be circumferentially freed and dissection carried distally to the level of the fifth or sixth intercostal arteries or in some cases even further to ensure minimal anastomotic tension.

When possible, the coarctation should be widely excised, including the segment in front of the stenosis. and the anastomosis carried out between the base of the arch and the descending thoracic aorta (Fig 2). To accomplish this, the descending thoracic aorta must be dissected free to allow it to be moved up to the arch. Dissection distal to the coarctation site is limited to the level of the first two or three pairs of intercostal vessels if patch aortoplasty is done.

The management of patent ductus arteriosus is determined by the technique of coarctation repair to be used. When resection is elected, the ductus is divided between fine vascular clamps

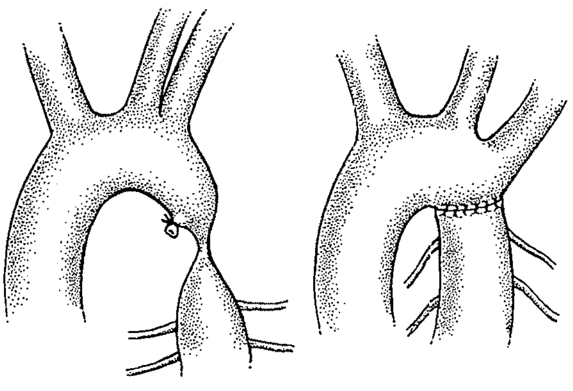

Fig 2. Coarctation repair using resection and end-to-end anastomosis.

and the divided ends are oversewn with continuous fine Dacron or polypropylene suture. If aortoplasty is done, the ductus is ligated in continuity with a No. 5 silk tie or a large hemoclip.

Fine microvascular instruments are used. If resection is chosen, the distal arch, left subclavian artery, and distal aorta are clamped. Intercostal vessels are controlled with doubly looped, temporary ligatures or microvascular clips. All involved aorta is resected. Repair is performed with a posterior continuous simple suture of 5-0 polypropylene and anterior interrupted simple sutures.

When Dacron patch aortoplasty is elected, proximal control is obtained with a single, fine, curved vascular clamp, which incorporates both the distal arch and the left subclavian artery (Fig 3). The aorta is opened longitudinally through the coarctation site with the incision carried proximally 2 to 4 mm into the origin of the left subclavian artery. The coarctation diaphragm is excised as completely as possible. A rectangular knitted Dacron patch of a width equal to the circumference of the descending aorta is selected, trimmed to a length of 1 to 2 cm longer than the aortic incision, and preclotted. The proximal end is tailored in elliptical fashion. The graft is sutured in place with a continuous 6-0 polypropylene or Dacron suture. Graft tailoring is completed when the proximal half of the suture line is in place. The remainder of the repair is then completed. Air is vented before the suture is tied. The clamps are slowly removed to prevent sudden hypotension. Hemorrhage is controlled with packs, and all blood loss is immediately replaced with warmed whole blood. In selected patients, pulmonary artery banding is performed if preoperative catheterization showed a large ventricular septal defect with pulmonary artery pressure greater than two-thirds of systemic pressure.

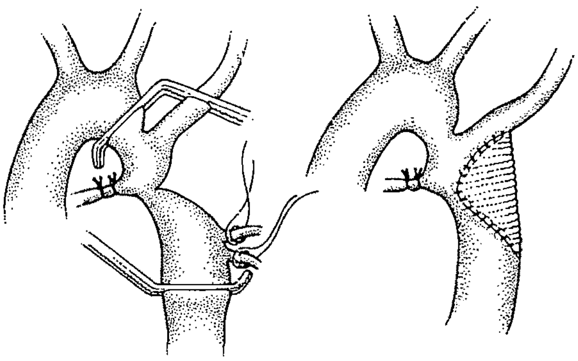

Fig 3. Coarctation repair using Dacron patch aortoplasty.

Results

Twelve of the 50 patients in this series who were operated on when they were 6 weeks old or less died—an overall mortality of 24%. There was 1 late death due to congestive heart failure in a child with complex congenital heart disease, two and one-half years following coarctation repair. The remaining 11 deaths took place during the perioperative period, for a 22% operative mortality. Two of these 11 deaths occurred intraoperatively and were attributable to hemorrhage or intractable cardiac rhythm abnormalities. In 2 patients, death was due to underlying metabolic derangement and cardiac arrhythmia. In the remaining 7 patients, death was directly related to ongoing cardiac failure secondary to the presence of one or more associated congenital cardiac anomalies.

Forty-five (90%) of the 50 infants had one or more associated congenital cardiac anomalies (Fig 4). The most frequently found lesions were patent ductus arteriosus (74%), atrial septal defect (74%), and ventricular septal defect (62%). Twenty-one patients (42%) had varying degrees of aortic arch hypoplasia. Seven of these infants died. Multiple lesions were present in all of the patients who died.

The follow-up period for the 38 survivors ranged from 3 months to eleven years with a

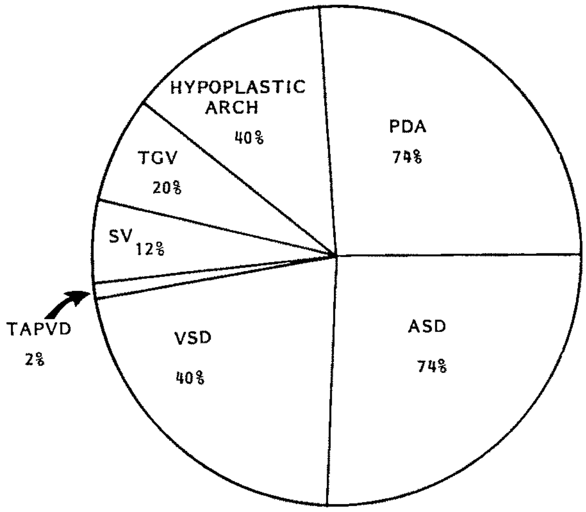

Fig 4. Associated congenital anomalies (frequency relative to each other and within the population). (PDA = *patent ductus arteriosus;* ASD = *atrial septal defect;* VSD = *ventricular septal defect;* TAPVD = *total anomalous pulmonary venous drainage;* SV = *single ventricle;* TGV = *transposition of the great vessels.)*

mean of 48.38 months. Data on clinical examination revealed good pedal pulses in 36 (95%) of the patients. In 17 patients (45%), upper and lower extremity blood pressure measurements were recorded. Two of the 38 (5%) had substantial upper extremity hypertension and an arm to leg pressure gradient in excess of 20 mm Hg. Both were female patients. A gradient of 30 mm Hg was noted in 1 when she was 10 weeks old. She had undergone repair when she was 4 weeks old. The patient was doing well clinically and was not recommended for reoperation. The other patient was repaired at 1 week of age. Fifteen months postoperatively, a gradient of 52 mm Hg was documented on examination. Due to the presence of increasing congestive heart failure, aortography was performed and showed stenosis at the site of repair. She underwent operative revision with good results and was the only patient to undergo reoperation during the follow-up period (2.6%). Both patients were seen early in the series and were originally repaired by resection and end-to-end anastomosis.

Comment

Considerable progress has been made in the surgical management of patients with coarctation since 1945 and 1946 when reports of successful repair were published [2, 6]. In 1960, Glass and associates [5] reported a 41% mortality among 34 patients operated on in the first year of life. Thirty-three of the repairs were done utilizing resection and primary end-to-end anastomosis. In the same series, 7 deaths (70%) occurred in 10 patients who had coarctation repair at less than 4 weeks of age. At follow-up, 11 patients (55%) had no resting postoperative hypertension or arm to leg gradient, while a gradient or hypertension or both were found in 9 (45%).

In 1967, Hallman and associates [7] cited a 21% operative mortality among 58 patients less than 1 year old when resection and end-to-end repair were used. Four additional patients died during the follow-up period of up to eleven years. Five of 42 patients available for follow-up had unsatisfactory results with 2 undergoing reoperation for recurrent coarctation at five and eight years after the original repair.

Tawes and co-workers [13] reported in 1969 the largest series of coarctation repairs in infants. One hundred seventy-nine of 333 patients were less than 1 year old at the time of operation. Operative mortality in this group was 45%. In a high-risk subgroup of 75 patients less than 6 weeks old, the operative mortality was 67%. Two hundred nine of the 333 patients were available for follow-up. Twenty (9.6%) had evidence of recoarctation. Nine (36%) of 25 survivors less than 6 weeks old were thought to have recoarctation. Ten patients out of the 209 survivors eventually underwent reoperation.

Macmanus and colleagues [9] in 1977 reported their experience with 44 infants less than 90 days old. They cited 14 operative and 8 late deaths, an overall mortality of 50%. Of 17 survivors with adequate follow-up data, 8 were considered to have excellent results, 4 to have fair, and 5 to have poor results. Four patients underwent early anastomotic revision, with 3 deaths. Reoperation was anticipated for 4 late survivors.

Herrmann and co-workers [8] in 1978 published a series of 25 patients less than 1 year old undergoing coarctation repair. There were 8 (32%) operative and 3 (12%) late deaths, for an overall mortality of 44%. The operative mortality in 18 patients less than 3 months old was

44%. Three of 17 early survivors had residual hypertension. Mortality in older age groups was minimal in all foregoing reports.

A review of our own experience was undertaken to evaluate our results with the highest risk group, those patients 6 weeks old and less. Among 50 neonates less than 6 weeks old, we had an operative mortality of 22% and 1 late death, an overall mortality of 24%. The incidence of residual arm to leg gradient or hypertension or both conditions, was 5% and 1 patient underwent operative revision during the follow-up period. We have used the definition of hypertension of Macmanus and associates [9] as being greater than 2 standard deviations above the mean pressure for age. These results compare very favorably with other series in the literature [5, 7–9, 13]. This fact has led us to evaluate our method of management.

The advisability of operation in these patients is rarely open to question. Mortensen and associates [10] reported a 64% mortality among 134 infants treated medically. Waldhausen and colleagues [15] reported a 75 to 100% medical mortality, depending on the presence or absence of associated intracardiac defects. Comparison of these findings with the operative result of this series and those previously quoted indicate that surgical treatment will be beneficial to this group of patients. We advocate early catheterization in patients who are seen with congestive heart failure and whose clinical examination suggests coarctation with or without associated congenital heart disease. Operation is performed immediately if the clinical impression is verified at catheterization. The neonatologists, cardiologists, and cardiovascular surgeons all participate in the rapid preoperative preparation of these patients.

Intraoperative management depends largely on an open, ongoing dialogue between the surgeon and anesthesiologist to "prevent" situations in which profound volume changes, hypoxemia, or hypotension may occur. If these situations do arise, immediate measures are taken rapidly to correct the underlying problem.

Postoperative care also is approached with a team concept and is usually delivered in a newborn intensive care setting where monitoring of the cardiac, respiratory, and metabolic status of each patient is most effectively carried out. We believe that each of these things has contributed importantly to the improved results indicated in our survival data.

The contribution of associated congenital cardiac anomalies to mortality and morbidity in these clinical situations is unmistakable. Hallman and colleagues [7] reported a 93% incidence of associated anomalies, with patent ductus arteriosus (93%) and ventricular septal defect (41%) being the most frequent. Glass and associates [5] similarly reported a 49% incidence of anomalies other than patent ductus arteriosus, including ventricular septal defect (33%), transposition of the great vessels (10%), and atrial septal defect (6%). Our own series is comparable in this regard with an overall incidence of 90%. Patent ductus arteriosus (74%), atrial septal defect (74%), and ventricular septal defect (62%) were the most commonly found lesions (see Fig 4). The number and severity of these lesions are major determining factors in the early onset and intractability of congestive heart failure and of mortality.

The 31 patients with coarctation and associated ventricular septal defect have presented a great management challenge due to the severity of congestive heart failure that prevails in this group. Nine (75%) of the deaths in our series occurred in this subgroup. It has been our practice to perform pulmonary artery banding in those patients who demonstrate a pulmonary artery pressure greater than two-thirds of systemic pressure at preoperative catheterization. Seventeen patients underwent coarctation repair in conjunction with pulmonary artery banding; there were 4 deaths, an operative mortality of 23%. Other groups report operative mortalities of 25 to 62% for this combined procedure [9, 14]. Presently, support is growing for concomitant or subsequent early open repair of ventricular septal defect in this setting [8]. While we agree that improved results in this area are needed, we have not been dissatisfied enough with our own experience to proceed with open repair of ventricular septal defect in these patients.

We have used Dacron patch graft aortoplasty since 1978. Reports by Reul [11], Fleming [3], Sade [12], and their associates utilizing this technique have indicated favorable results. We have been impressed by the relative ease of performance and utility of the technique, particularly in situations involving hypoplasia of the aortic isthmus. There were no complications referable to the use of this procedure in our patient group.

Comparison of the group repaired using resection and end-to-end anastomosis with the group having Dacron patch aortoplasty reveals no concrete evidence that would recommend one procedure over the other. Overall mortality was 26% for resection versus 22% for aortoplasty. The incidence of associated anomalies was essentially the same in each group. The follow-up period for our aortoplasty group is not yet long enough to allow us to draw a meaningful comparison concerning recurrence. It is our impression, however, that patch aortoplasty will reduce the incidence of a gradient across the repair if patients are exercised.

There are several technical points concerning the technique of patch aortoplasty that deserve emphasis. In performing the aortotomy, the incision must be carried well into the subclavian artery and well beyond the site of coarctation on the descending aorta. These maneuvers will place the widest portion of the carefully tailored patch graft at the outlet of the distal transverse aortic arch and the coarctation segment, avoiding narrowing in both of these critical areas. Attention to this aspect of technique in the performance of aortoplasty can abolish pressure gradients even in instances of severe isthmus hypoplasia.

The choice of prosthetic material is another point of controversy. We regard Gore-Tex as an attractive prosthetic but have been concerned about potential aneurysm formation, as reported by Campbell and colleagues [1] in 1976. We have chosen knitted Dacron for use in these patients because of its longer period of demonstrated safety and its ease of handling. Knitted Dacron is soft and pliable and conforms well to the neonate's delicate aorta.

The method of subclavian angioplasty as reported by Waldhausen and Nahrwold [16] at our institution has been used sparingly for several reasons. It has been our impression that the vessel is often of inadequate width and length to allow proper repair. Also, we have been hesitant to use this technique when alternative techniques have proved to be adequate and we can avoid the possible complications of subclavian division, namely, negative effects on arm growth, possible subclavian steal syndrome, and Horner's syndrome. In addition, the procedure involves added operating time in situations where this can be ill-afforded.

The lower incidence of residual blood pressure gradients (5%) and need for reoperation (2.6%) presented here compare very favorably with other published reports [5, 7–9]. We think these results are based primarily on strict adherence to details of operative technique in performing either end-to-end or patch aortoplasty repair. Only further follow-up will determine whether these numbers hold true in the long term, particularly in the very young patients considered here.

In summary, we have presented our experience with coarctation repair in the newborn less than 6 weeks old, a highly complicated patient group. Our results in terms of mortality and lowered recurrence have been gratifying. We believe that a concerted team approach to patient management, early operation, and strict adherence to careful operative technique are the keys to success with these infants.

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Discussion

DR. ROBERT M. SADE (Charleston, SC): I congratulate the authors on a well-analyzed and well-presented series, as well as on their fine results in this difficult group of patients. I fundamentally agree with their techniques and with their conclusions, but do have a few technical disagreements.

First, I don't think it is necessary to dissect the intercostal arteries. Doing so prolongs the operation a bit and increases the risk of injury to those vessels. Therefore, I don't dissect any intercostal arteries.

We use Gore-Tex rather than Dacron for patching in small infants because Gore-Tex has a very thin neointima. In the small vessels of infants, this kind of neointima may contribute to maintenance of patency and less gradient late postoperatively. A microscopic view of a Gore-Tex patch recovered a year after implantation showed the thin neointima that can be measured in microns rather than millimeters, as is often seen with Dacron.

The major problem with this paper was the methodology of follow-up, as I think the authors recognize. In all the patients, blood pressure was measured in the upper extremity and pedal pulses were palpated, but in only 45% was there measurement of both upper and lower extremity pressures. Furthermore, none of the patients had either cardiac catheterization or exercise testing to measure gradients. On the basis of these rather thin follow-up data, the authors were correct in saying that they cannot conclude that one kind of operation is better than another.

We presented to this Society last year data that indicate clearly that patch aortoplasty, whether subclavian flap or Gore-Tex or Dacron, is superior to end-to-end anastomosis. This was suggested, though not proved, by the data we just heard.

For future follow-up of patients undergoing this repair, it will be inadequate simply to measure blood pressure or even to measure pressure differences between upper and lower extremities. We are going to have to do exercise testing, as suggested by Michael Freed at Boston Children's Hospital a couple of years ago. We have done exercise testing of our patients who underwent coarctation repair in the past couple of years and have found that many who have no resting pressure gradient and no hypertension, on exercise testing have very significant pressure gradients, sometimes in the range of 50 to 60 mm Hg. Significant hypertension also develops, indicating that they have residual narrowing at the coarctation site. This narrowing is simply not detectable by hemodynamic measurements taken during the resting state.

I ask the authors whether they have any data gathered during exercise in their patients that allows comparison between patch grafting and end-to-end anastomosis.

DR. WILLIAM H. FLEMING (Omaha, NE): I, too, congratulate the authors on their very excellent results and on a careful analysis. We have been using this technique for about five years, and it works. Out of 40 patients, 2 have died. One died of digitalis toxicity 5 days postoperatively and 1, of bowel perforation 6 weeks postoperatively.

I want to point out several things we have found on longer follow-up. First, most of our patients have been recatheterized now, and they do not have gradients at the repair site. A few of them will have gradients on the hypoplastic isthmic portion of the aorta.

Second, in infants with intact ventricular septum and critical coarctation, there may be absolutely dreadful left ventricular function. Don't be deterred by it. Talk to the anesthesiologist, go carefully, and keep following the ejection fraction with echo. It is amazing the recovery those ventricles will show in just a few days. By the time the child is ready to go home, they will be back to normal ejection fraction. I was delightfully startled by that.

Third, 2 patients now have calcified patches. These patients were catheterized a second time and have perfectly normal flow. There is no problem from the calcification that we know of, but the patches are calcified on plain roentgenogram. I don't know where that leads us.

Finally, when it is time to close the ventricular septal defects in the patients with this accompanying condition, be very sure to have a good definition of the anatomy; at least a quarter of the children will have an unusual ventricular septal defect, for example, muscular or multiple.

DR. BROWN: I thank the discussants. Also, I will update our data by reporting that 10 more neonates have undergone repair without mortality at our institution since we submitted the abstract.

In response to Dr. Sade, we do not sacrifice intercostal arteries but we do control the first pair in order to expose a very large segment of aorta. We are aware of Dr. Sade's clamp and look forward to seeing it and possibly using it in the near future. We also are attracted to Gore-Tex as a graft material but await others' experience before we undertake its use as our routine prosthetic material.

We are aware of the current inadequacies of our follow-up data in newborns following coarctation repair. Currently, we and our cardiologists are engaged in an extensive evaluation of this series and are doing exercise testing on all of these patients.

We are encouraged by Dr. Fleming's long-term follow-up of Dacron patch angioplasty. This has stimulated us to continue our current patching technique. We have not yet seen calcification of Dacron patches, but, again, our follow-up is relatively short.

Our experience with closure of ventricular septal defect in patients less than 6 weeks old has been very limited. Published results of closure in this very young age group deter us from undertaking primary closure as a routine practice at the present time.

Positive End-Expiratory Pressure in the Management of the Patient with a Postoperative Bleeding Heart

Patricio A. Ilabaca, M.D., John L. Ochsner, M.D.,
and Noel L. Mills, M.D.

ABSTRACT **This prospective study involves 406 consecutive adults who had heart operation with extracorporeal circulation. Fifteen patients (3.7%) bled at the rate of 200 ml per hour or more in the postoperative period. Thirteen of the 15 patients who bled had undergone coronary artery operation.**

After all clotting factors and, when applicable, hypertension had been checked and corrected, positive end-expiratory pressure (PEEP) was used in managing the bleeding of these patients. Before institution of PEEP, the average bleeding was 330 ml per hour for one to five hours. After PEEP was instituted in the 11 patients in whom bleeding was controlled, an average output of 25 ml per hour for one to ten hours was recorded. Patients were kept on PEEP for five to ten hours.

In 7 patients hemorrhage was controlled with 10 cm H_2O of PEEP; 4 required 15 cm of PEEP to stop bleeding; 3 were explored for continuous bleeding on 15 cm of PEEP; and 1 was explored because of hypotension on 15 cm of PEEP. In 11 of the 15 patients who bled postoperatively (73%), operation was avoided by judicious use of PEEP. We believe that PEEP increases mediastinal pressure and that the overdistended lung can obliterate some bleeding in the mediastinum, thus controlling bleeding in many of these patients.

Hemorrhage is a rare but serious complication of surgical procedures. If reoperation is required, the risk is increased and there is greater possibility of wound infection. Positive end-expiratory pressure (PEEP) increases mediastinal pressure and hyperinflates the lung. This measure may reduce mediastinal hemorrhage. Therefore, PEEP was used to treat postoperative bleeding if it occurred after heart procedures done with extracorporeal circulation.

Materials and Methods

Four hundred six consecutive adults who had heart operation with extracorporeal circulation at Ochsner Foundation Hospital were included in this study. Fifteen patients (3.7%) bled at a rate of 200 ml an hour or more in the early postoperative period. PEEP was used in the management of the bleeding. There were 12 men and 3 women in the group. Thirteen had coronary artery operation, 1 had closure of an atrial septal defect, and 1 had replacement of a mitral prosthesis (Hancock) for infective endocarditis. The mediastinum was drained with two No. 24 Saratoga sumps (Figure) connected to 120 to 160 mm Hg suction, and in those patients in whom the pleura was entered, a No. 32 Argyle tube was used to drain the pleura. To avoid potential problems derived from the vacuum power of sumps, the anterior tube is left below the proximal suture line in coronary artery bypass patients, and the posterior tube is directed toward the left ventricular apex with a loose stitch of Dexon.

Activated clotting time (ACT) was monitored in all patients after protamine was given intraoperatively and if bleeding was excessive, postoperatively. If the ACT was prolonged, protamine was given until it came within the normal range of 120 to 140 seconds. All patients had determination of prothrombin time (PT), partial thromboplastin time (PTT), and platelet count in the intensive care unit. We did not routinely study fibrinogen levels or platelet adhesiveness.

Fresh-frozen plasma was given empirically to some patients during the bleeding episode. Those patients who were hypertensive while bleeding (170 to 210 mm Hg systolic) were

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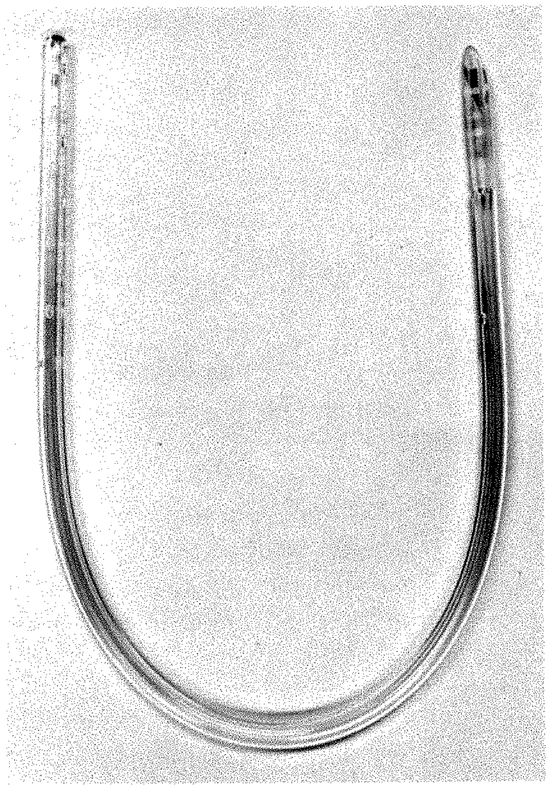

Saratoga sump.

treated with pentolinium (Ansolysen) to lower the pressure to 100 to 120 mm Hg systolic. Volume was replaced with whole blood and human serum albumin (Plasmatein).

When the patient met our criteria for exploration of the mediastinum for postoperative hemorrhage, PEEP was instituted. All patients were started on 10 cm H_2O of PEEP, but when 10 cm did not control or decrease the rate of hemorrhage, the pressure was increased to 15 cm H_2O. If bleeding continued on 15 cm of PEEP and in 1 patient who became hypotensive on it, the mediastinum was explored.

Results

Of the 15 patients who bled, 2 required extra doses of protamine in the intensive care unit because of prolonged ACT; however, bleeding continued after it was corrected and stopped only after PEEP was begun. PT and PTT were within normal limits in all patients, and a platelet count less than 110,000/mm^3 was not recorded. The administration of fresh-frozen plasma and platelets did not change the rate of bleeding in this group of patients. Four patients required pentolinium to lower the blood pressure, but this alone did not stop the bleeding. The chest roentgenograms of these patients showed no mediastinal enlargement or pleural fluid levels, and no patient had tamponade while bleeding.

In 7 patients, hemorrhage was controlled with 10 cm of PEEP. Four patients required 15 cm to stop bleeding. Three patients were explored for continuous bleeding on 15 cm of PEEP and 1 patient because of hypotension when PEEP was increased from 10 to 15 cm H_2O.

The bleeding sources in 3 of the 4 patients who required reoperation were (1) two branches of a saphenous vein graft, (2) a branch of the right internal mammary artery severed at the upper third of the sternum, and (3) a large vein severed at the right side of the xiphoid. In the fourth patient, no definite site was found. After reexploration, 10 cm of PEEP was started again. The patient continued to bleed (450 ml in three hours). When PEEP was increased to 15 cm H_2O, the bleeding stopped instantaneously (30 ml over eight hours).

These 15 patients were their own control. Before institution of PEEP, the bleeding averaged 320 ml per hour (range, 230 to 610 ml per hour) and lasted from one to five hours. In the 11 patients in whom bleeding was controlled by PEEP, an average of 25 ml per hour from one to ten hours was recorded (range, 5 to 100 ml per hour) (Table). The decrease in the bleeding rate was noted in all patients within one hour after PEEP was instituted. PEEP was maintained for five to ten hours and then progressively discontinued. No patient bled again during weaning, and there was no PEEP-related complication.

Comments

Mechanical ventilation to produce PEEP is widely used to treat adult respiratory distress syndrome, and the mechanism by which it improves partial pressure of oxygen has been reported [4, 8, 9]. The use of PEEP to control hemorrhage after open-heart operations has not been reported to our knowledge.

Mediastinal Drainage before and after Positive End-Expiratory Pressure in Patients in Whom Bleeding Was Stopped with This Treatment

Patient No.	Before (ml/hr)	After (ml/hr)
1	260	5
2	250	10
3	250	20
4	500	100
5	250	8
6	230	10
7	375	55
8	250	40
9	350	20
10	310	30
11	340	25

Approximately 25% of our patients who bled were hypertensive in the immediate postoperative period. Although hypertension can be a factor in initiating or maintaining bleeding, none of our patients stopped bleeding when the blood pressure was brought to normotensive levels. Blood pressure must be lowered in these patients, not only because of bleeding, but also to decrease the left ventricular afterload. Although most centers give sodium nitroprusside (Nipride) to lower pressure, we used pentolinium because it can be given rapidly intravenously and can be counteracted almost instantaneously with calcium. Usually one or two doses three to four minutes apart will lower the blood pressure to the desired level. Unfortunately, pentolinium is not commercially available in the United States at present.

A number of studies related deficiency in coagulation factors and thrombocytopenia to cardiopulmonary bypass [2, 5, 6, 11]. Our investigation of clotting factors was not extensive, but we did find that PT and PTT were normal in all patients; ACT was prolonged in only 2 patients (corrected with protamine), and the platelet count was above 100,000/mm^3 in all patients. In 21 patients with postoperative bleeding reported by Bachmann and co-workers [1], 15 patients had no laboratory evidence of abnormal coagulation and 13 of those had a bleeding site identified at reoperation. On the other hand, of 29 with some coagulation abnormality, only 4 bled excessively after operation.

Some authors believe that disseminated intravascular coagulopathy (DIC) is responsible for the thrombocytopenia and coagulation factor deficits observed after cardiopulmonary bypass [3, 10]. If drainage is not adequate, clot formation in the pericardium and mediastinum can trigger low cardiac output and possibly DIC and fibrinolytic hyperactivity. We believe that sump drainage of the mediastinum with Saratoga tubes is far more efficient than drainage with regular chest tubes. Sump drainage, therefore, may be an important point in preventing coagulation factors and platelet consumption in our patients by allowing normal hemodynamics with adequate blood replacement.

Complications related to PEEP did not occur. All patients tolerated a PEEP of 10 cm H_2O. Three of the 4 who required 15 cm of PEEP tolerated it well; 1 did not tolerate it, possibly because of hypovolemia.

Many of our patients received a left internal mammary artery bypass to the anterior descending coronary artery or a diagonal branch [7]. Overdistention of the lung by PEEP can disrupt this anastomosis, if the mammary graft is not of sufficient length. Therefore, before closing the chest, we routinely check the effect of the lung on the mammary graft with a PEEP of 10 and 15 cm H_2O.

In the 11 patients whose bleeding was stopped by PEEP, the source of bleeding remains unknown. In 3 of the 4 who required reoperation, a definite surgical bleeder was found. In the fourth patient, no definite site was found and the bleeding continued postoperatively, stopping only when 15 cm H_2O of PEEP was used.

Although this method may not stop bleeding from arterial branches, large veins, or a leaking suture line, clearly it can control diffuse bleeding by distending the lungs, which increases mediastinal pressure. All of the 15 patients who bled postoperatively would have had reoperation for excessive hemorrhage if PEEP had not been used in their management. In 11 patients

(73%), reoperation was avoided by judicious use of PEEP. We conclude that PEEP is a valuable tool in the treatment of bleeding that occurs after heart operations with extracorporeal circulation.

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An Improved Technique for Producing Ventricular Hypertrophy with a Subcoronary Valvular Aortic Stenosis Model

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Ronald C. Hill, M.D., Gary L. Pellom, B.S., and Andrew S. Wechsler, M.D.

ABSTRACT **Although techniques for producing aortic valve stenosis proximal to the ostia of the coronary arteries have been described in experimental animals, only moderate left ventricular hypertrophy has been obtained. A technique for plicating the noncoronary sinus of Valsalva in puppies is presented that has enabled us to achieve levels of ventricular hypertrophy not previously reported with methods for subcoronary aortic stenosis.**

Recently, techniques have been described for plicating the noncoronary sinus of Valsalva in dogs to produce aortic valve stenosis proximal to the ostia of the coronary arteries [1, 2]. Although these methods successfully reproduced the coronary hemodynamics present with aortic stenosis, only moderate left ventricular hypertrophy was obtained. We have developed a modification of previously described techniques that has enabled us to achieve levels of left ventricular hypertrophy not before obtained by external plication of the noncoronary sinus of Valsalva.

Method

General anesthesia was induced in 17 puppies weighing 2.5 to 5 kg by intravenous injection of thiamylal sodium (5 ml with 0.025 gm per milliliter), supplemented as needed. Following intubation, the animals were ventilated with a Harvard respirator. A thoracotomy was performed in the right fourth intercostal space, and the pericardium was opened over the right atrium and proximal aorta. The right atrial appendage was retracted caudally, and the base of the right atrium was dissected from the right side of the aorta from the level of the interatrial septum posteriorly to the origin of the right coronary artery anteriorly. Following proper dissection, the entire noncoronary sinus should be visible.

Then a partial occlusion clamp was placed on the ascending aorta, and the aorta was retracted cephalad and to the right, bringing the noncoronary sinus into better view. A single double armed 3-0 Prolene vascular suture with Teflon felt pledgets was used to completely obliterate the noncoronary sinus and valve. The needle entered the aorta at the left posterior extreme of the sinus at a level proximal to the left coronary artery ostium and exited proximal to the right coronary ostium at the right posterior extreme of the sinus. The second needle was placed in the aorta in the same plane in a more anterior position. A second Teflon felt pledget was threaded over the suture, which was then tied down tightly (Fig 1). Bleeding from the needle holes was controlled by the pledgets as the suture was tied. The entire sinus from commissure to commissure can be easily plicated with one suture in dogs of this size.

Following plication, a thrill usually was palpable easily within the aorta. No effort was made to monitor aortic or ventricular pressures. After the pericardium was closed, the chest was closed in three layers using a chest tube to evacuate the pneumothorax. Hemorrhage occasionally occurred from a tear in the right atrium, usually the result of too vigorous retraction on the atrium. In one animal, there was bleeding from the right atrium secondary to a laceration, which occurred as the atrium was being dissected from the aorta. The puppies seemed to tolerate the acute left ventricular pressure increase easily; however, 3 animals

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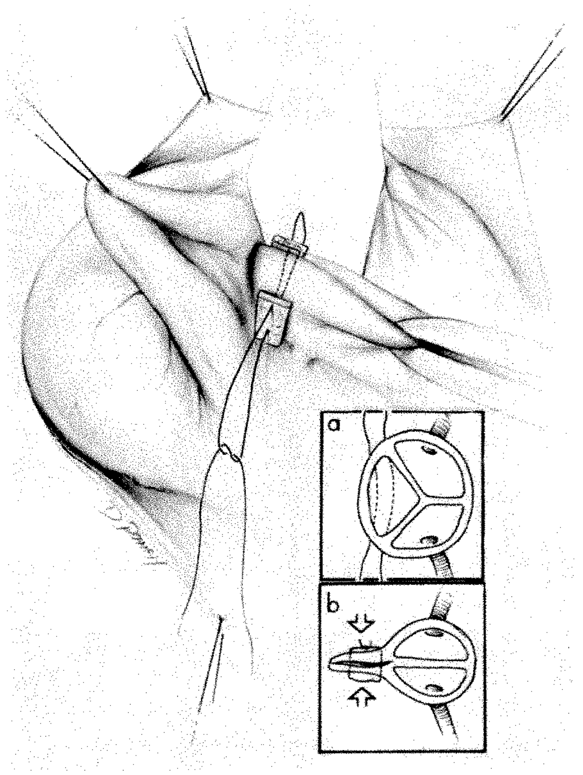

Fig 1. Placement of the sutures and pledgets proximal to the coronary ostia for obliteration of the noncoronary valvular sinus.

experienced acute left ventricular failure. Although 2 of these animals died during operation, in the third animal the suture was removed and replaced successfully. We had no difficulty with the previously reported complication of atrioventricular block resulting from damage to the conducting system as it passes through the intraventricular septum [1].

Results

All dogs were studied four to six months following the initial procedure. Of the 17 dogs operated on, 11 (65%) survived to the time of the study. Survivors were active at the time of study with no evidence of heart failure or aortic insufficiency. Of the 6 dogs that died, 5 died during operation, 3 of hemorrhage due to a right atrial tear and 2 of acute left ventricular failure due to overstenosis. One dog was found dead in his cage two months following the initial procedure; no anatomical cause of death could be demonstrated. No dogs exhibited evidence of endocarditis, atrioventricular fistulas, or heart block.

One dog underwent cardiac catheterization four months following the procedure. Figure 2 demonstrates a 60 mm Hg pressure gradient between the left ventricle and the ascending aorta. Data from the same animal demonstrate that the left main coronary artery pressure is identical to the pressure of the ascending aorta at the level of the coronary ostia (Fig 3). Selected angiograms demonstrate clearly that the stenotic valve is proximal to the right and left coronary ostia (Fig 4).

Hypertrophy was assessed by the ratio of left ventricular weight to body weight (grams per kilogram). The Table gives the anatomical data from the 11 dogs with aortic stenosis compared with normal values. The mean left ventricular body weight ratio in the dogs with aortic stenosis was 7.59 compared with a normal value of 4.43. Figure 5 demonstrates the marked left ventricular wall thickening four months following operation compared with a left ventricle from a dog that did not undergo operation.

Comment

Although techniques have been described recently for producing subcoronary aortic stenosis, only moderate left ventricular hypertrophy has been obtained [1, 2]. The ratio of mean left ventricular weight to body weight in our group of hypertrophied dogs was 7.59, while none of the animals reported by Allard and colleagues [1] had a ratio of this magnitude. Roper and co-workers [2] did not provide this ratio. The mortality associated with our technique was 35%, while Allard and colleagues [1] reported a mortality of 46% and Roper and associates [2], a 30-day mortality of 33.3%. Therefore, by modifying previously reported techniques for use in puppies, we have produced greater hypertrophy with an acceptable mortality. The initial stenosis probably becomes relatively more severe as the puppy grows, and results in larger gradients and greater hypertrophy. In summary, we have reported a technique for the production of subcoronary aortic stenosis which is simple, fast, and well tolerated, and which results in massive left ventricular hypertrophy in a reasonable period of time.

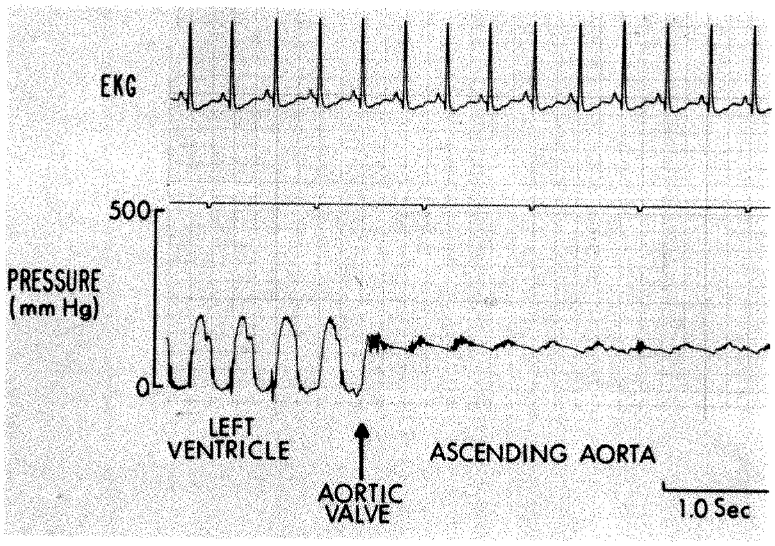

Fig 2. "Pullback" pressure tracing demonstrating a 60 mm Hg pressure gradient between the left ventricle and the ascending aorta.

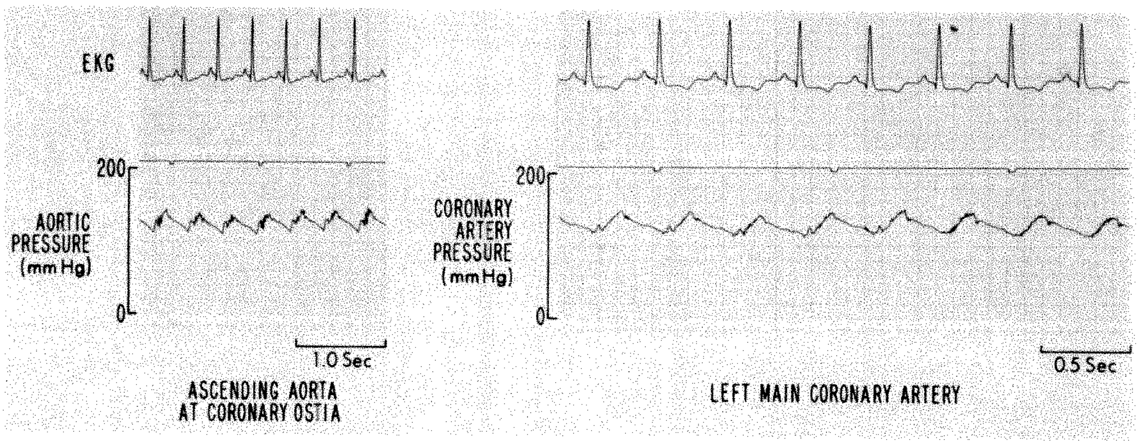

Fig 3. The left main coronary artery pressure is identical to the ascending aorta pressure, thereby confirming the subcoronary position of the stenosis.

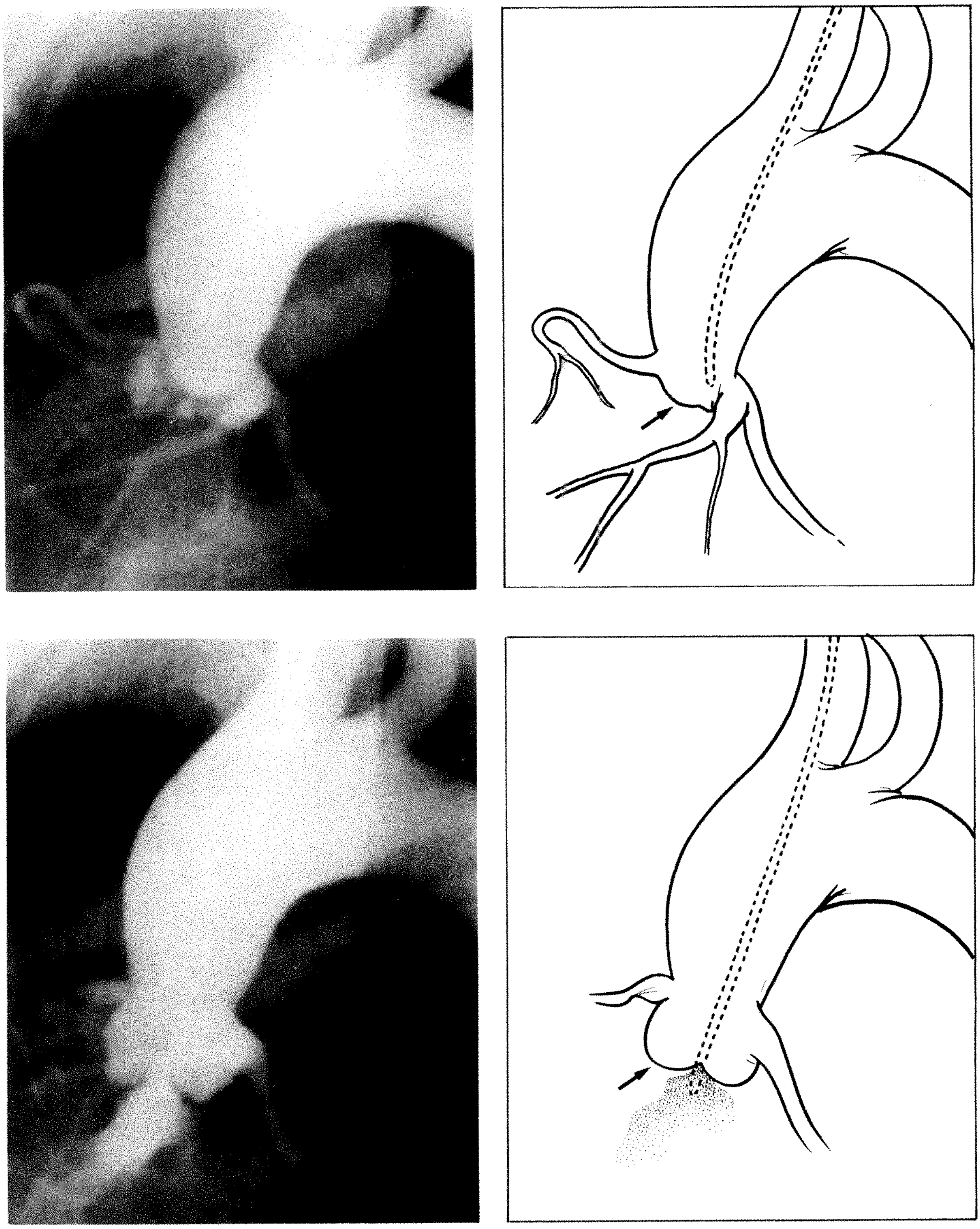

Fig 4. Angiograms, and line interpretations, made four months following operation demonstrate that the stenotic valve is proximal to the coronary ostia.

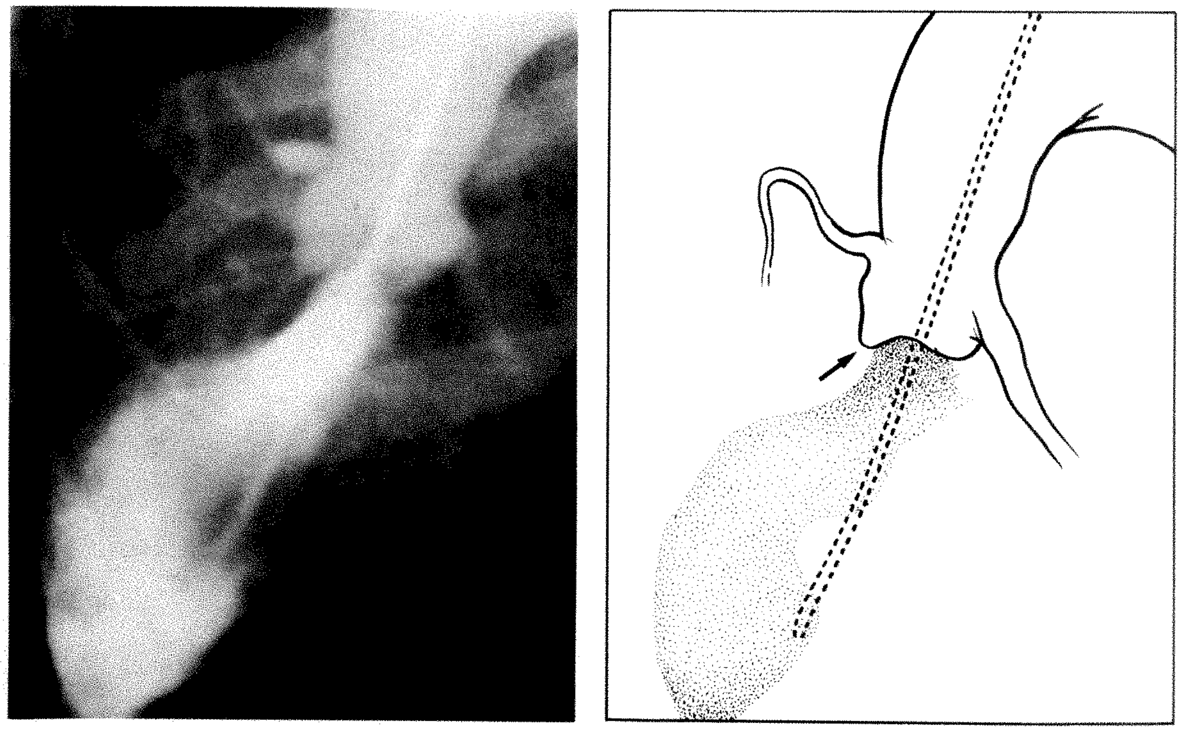

Fig 4. (Continued)

Anatomical Data

Dog No.	Body Weight (kg)	LV Weight (gm)	LV/Body Weight Ratio (gm/kg)
1	20.5	112.5	5.45
2	14.5	86.5	4.96
3	9.5	74	7.77
4	12.7	103.5	8.15
5	15.5	105	6.77
6	19.9	139.2	6.97
7	12.9	136.7	10.57
8	14.6	100	6.84
9	11.0	91.4	8.31
10	9.3	84.1	9.04
11	12.0	91.7	7.63
Mean	13.9	102.2	7.59
± SEM	1.1	6.2	0.43
Normal value	14.3	63.3	4.43

LV = left ventricular; SEM = standard error of the mean.

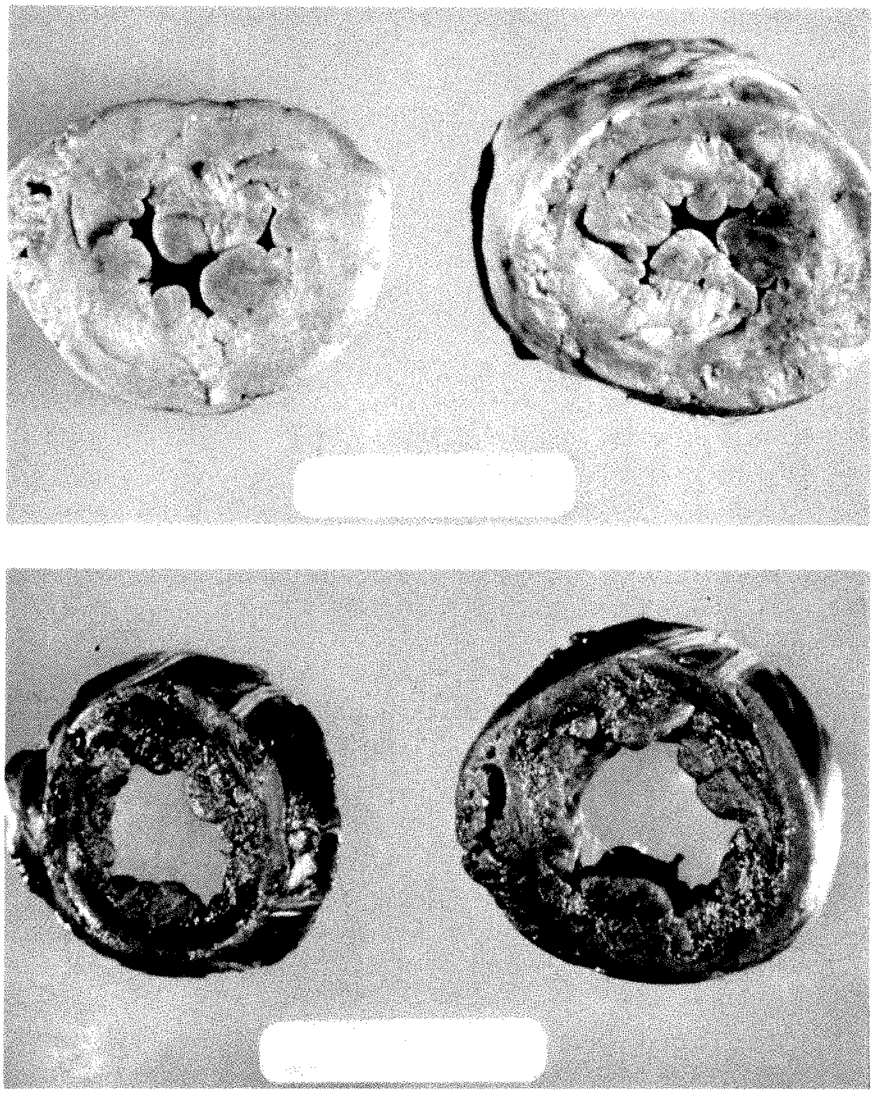

Fig 5. Aortic stenosis resulted in marked left ventricular wall thickening (upper panel). The lower panel is a left ventricle from a normal dog.

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External Stent for Repair of Secondary Tracheomalacia

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Larry W. Stephenson, M.D., and L. H. Edmunds, Jr., M.D.

ABSTRACT **Tracheomalacia was created in anesthetized piglets by submucosal resection of 3 to 5 tracheal cartilages. Measurements of airway pressure and flow showed that expiratory airway resistance is maximal at low lung volumes and is significantly increased by creation of the malacic segment. Cervical flexion increases expiratory airway resistance, whereas hyperextension of the neck reduces resistance toward normal. External stenting of the malacic segment reduces expiratory airway resistance, and the combination of external stenting and hyperextension restores airway resistance to normal except at low lung volume.**

Two patients with secondary tracheomalacia required tracheostomy and could not be decannulated after the indication for the tracheostomy was corrected. Both were successfully decannulated after external stenting of the malacic segment with rib grafts. Postoperative measurements of expiratory pulmonary resistance show a marked decrease from preoperative measurements. External stenting of symptomatic tracheomalacia reduces expiratory airway resistance by supporting and stretching the malacic segment and is preferable to prolonged internal stenting or tracheal resection.

Secondary tracheomalacia is an acquired weakening or incomplete formation of the cartilaginous rings due to external compression [1, 20]. In infants, vascular rings, anomalous innominate or left carotid arteries, tracheoesophageal fistulas, or mediastinal masses may cause secondary tracheomalacia. After surgical relief of the external compressing structure, the malacic segment of trachea may continue to produce obstructive symptoms due to a dynamic narrowing of the lumen during expiration [2, 3, 6, 11]. Primary tracheomalacia, in contrast, appears to be a congenital defect in tracheal maturation leading to softening of the cartilaginous rings [1]. Both conditions may cause marked respiratory distress; however, primary tracheomalacia is usually self-limiting and symptoms gradually resolve by the time the patient is 2 years old [1, 14].

Both primary and secondary tracheomalacia are lesions of the intrathoracic trachea causing expiratory airway obstruction. In contrast, laryngomalacia and the malacic area associated with a tracheostomy stoma are extrathoracic and cause obstructive symptoms during inspiration [5, 21].

To study intrathoracic tracheomalacia we created an animal model and noted the effects of neck flexion, neck extension, lung volume, and external stenting on airway mechanics. Here we report these findings and the cases of 2 patients with symptomatic tracheomalacia following vascular ring division who were successfully treated by external stenting.

Materials and Methods

Tracheomalacia was created in 6 piglets (mean weight, 3.4 kg) by submucosal resection of 3 to 5 intrathoracic tracheal cartilages through a low midline cervical incision during halothane anesthesia. The malacic segment was stabilized by a rigid external prosthesis fixed to normal tracheal cartilages above and below the malacic segment. Sutures passed through the exposed mucosa were tied over the stent. Airflow was measured through a cervical tracheostomy with a pneumotachograph (Hewlett-Packard model HP21069B), rated at 0.05 L/sec/volt. A modified 21 gauge butterfly needle (Abbott Hospitals, Inc.), inserted through the trachea perpendicular to airflow below the malacic segment, recorded intratracheal pressure. Differences between distal tracheal pressure and ambient pressure were measured by a differential pressure transducer* (Hewlett-Packard

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model 270). Tidal volume was determined from the flow curve using a respiratory integrator (Hewlett-Packard model 8815A). All measurements were simultaneously entered on a four-channel recorder (Hewlett-Packard model 47601A).

Three arbitrary points on the expiratory slope of the tidal volume curve were chosen for comparison at 20, 10, and 4 ml above functional residual capacity (FRC). Expiratory airway resistance (RE) was then calculated at the three volumes in the normal trachea, after creation of the malacic segment, and after external stenting using the formula: $R_E = \Delta Paw/\dot{V}$ [8], where ΔPaw = differences between distal tracheal pressure and ambient pressure and $\dot{V}$ = airflow. Measurements were made with the trachea in two positions: flexed and hyperextended to simulate the extremes of neck mobility.

In patients, flow was measured by attaching a pneumotachograph (Hewlett-Packard model HP21071B), rated at 0.05 L/sec/volt, to the tracheostomy tube, which was positioned above the malacic segment preoperatively. Postoperatively, flow was measured through an endotracheal tube with the tip positioned just below the larynx. Resistance was calculated from the difference between atmospheric pressure and intrathoracic pressure as measured at zero flow [9].

Results

Creation of tracheomalacia in piglets significantly increased RE with the trachea in the flexed position (Table 1). The normal increase in RE as expiratory volume approached FRC [8] is seen in the control data. This increase is illustrated at the three arbitrary lung volumes on the expiratory slope of the tidal volume curve (Fig 1A). Since the average tidal volume was 42.2 ml, these points represent RE at approximately 50%, 75%, and 90% of expired volume. Stenting the malacic segment returns RE toward control values (see Table 1).

Expiratory airway resistance of the normal trachea does not change significantly when longitudinal tension is placed on the trachea at the cervical tracheostomy site to simulate

Table 1. Expiratory Airway Resistance in Piglets at Three Lung Volumes

Position	V from FRC (ml)	RE (cm H_2O/L/sec)[a] Control	Malacic	Stented
Trachea flexed	20	7 ± 2.8	21 ± 13.8^{c}	11 ± 4.5^{e,h}
	10	10 ± 3.8	26 ± 14.5^{b}	16 ± 7.2^{e,g}
	4	16 ± 4.4	29 ± 10.4^{b}	21 ± 8.5^{f,g}
Trachea Hyperextended	20	8 ± 2.4	10 ± 2.6^{d}	8 ± 1.9^{f,h}
	10	11 ± 3.3	13 ± 3.4^{d}	12 ± 2.8^{f,i}
	4	15 ± 2.5	19 ± 2.8^{c}	21 ± 6.4^{e,i}

[a] Mean ± standard error of the mean. The p values were calculated by the paired t test. Superscripts b, c, and d indicate comparison between control values and malacic segments; e and f, between control values and stented segments; and g, h, and i, between malacic and stented segments. Significant values: ^{b,g} = $p < 0.05$; ^{c,e,h} $p < 0.1$; ^{d,f,i} = not statistically significant. N = 6 in all groups.

V = volume; FRC = functional residual capacity; RE = expiratory airway resistance.

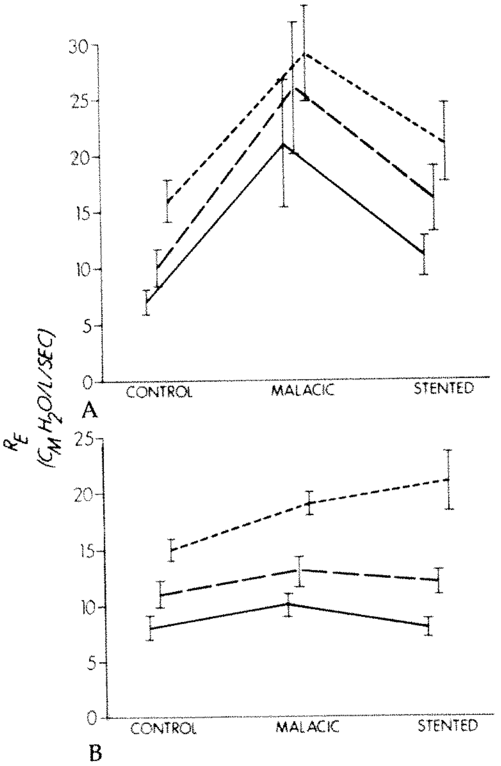

Fig 1. Average expiratory resistance (R_E) in 6 piglets with the trachea (A) flexed and (B) hyperextended. Comparisons are made at three volumes: before creation of the malacic segment, after creation of tracheomalacia, and after stenting the malacic segment with an external stent. (•———• = lung volume (V) 20 ml > functional residual capacity (FRC); •— —• = V 10 ml > FRC; •------• = V 4 ml > FRC; vertical bars indicate standard error of the mean.)

hyperextension of the neck. With simulated hyperextension, RE increases slightly after creation of the malacic segment (Fig 1B). Except at the lowest lung volume, the combination of stenting and simulated hyperextension reduces RE more effectively than either manuever alone (see Table 1, Fig 1).

Case Reports

Patient 1

A 5-year 5-month-old boy underwent division of a double aortic arch when he was 4 months old. After operation, respiratory failure and expiratory stridor required reinsertion of the endotracheal tube past the malacic segment. Tracheostomy was performed several weeks later. After five months of mechanical ventilation, he was eventually weaned from the respirator and discharged home with the tracheostomy tube in place. Multiple attempts at decannulation in the ensuing four years were unsuccessful. Bronchoscopy and lateral chest fluoroscopy consistently revealed segmental tracheomalacia at the level of the transected vascular ring (Fig 2).

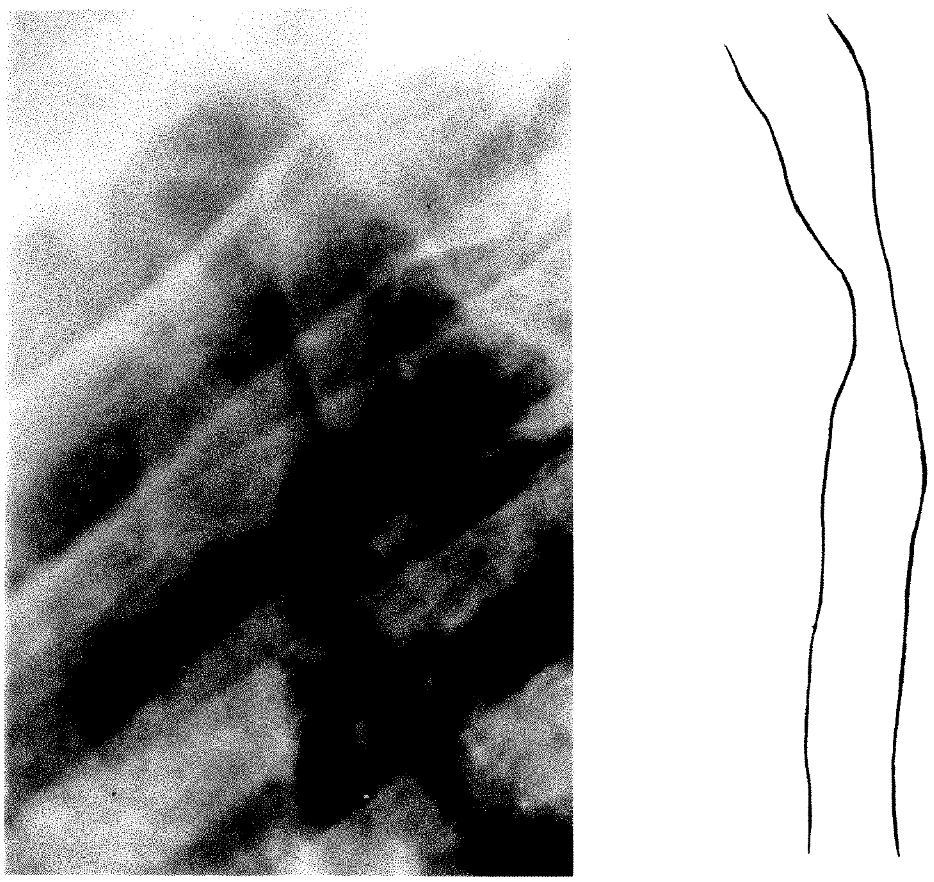

Fig 2. (Patient 1.) Lateral roentgenogram and line interpretation of the trachea during expiration. Tracheal narrowing is present at the site of the previously divided vascular ring.

External stenting of the malacic segment was performed when the patient was 4 years 10 months old. A left anterolateral thoracotomy was utilized because of the right aortic arch. After the distal trachea and carina were mobilized, the malacic cartilages were identified. A piece of excised rib was split longitudinally and cut to an appropriate length for use as a stent. Sutures of 4-0 Prolene placed through the malacic cartilage and through normal cartilage above and below the malacic area were then tied over the rib stent. The most cephalad sutures were anchored to the underside of the sternum.

Following placement of the external rib stent, decannulation was accomplished uneventfully, and the patient was discharged on the tenth postoperative day. Peak expiratory flow rate increased from 26 L/min preoperatively to 48 L/min postoperatively.

Patient 2

An 18-month-old girl at age 3 months had division of a vascular ring, which was causing marked dyspnea and difficulty in feeding. A right ligamentum arteriosum associated with a left aortic arch and right descending thoracic aorta was divided through a right thoracotomy. Cardiac catheterization revealed agenesis of the left pulmonary artery and a large ventricular septal defect. The patient's respiratory status gradually improved after operation, and she was discharged home with only mild respiratory insufficiency.

During the next six months the patient had multiple admissions for lower respiratory infections, congestive heart failure, and failure to thrive. When she was 10 months old, the ventricular septal defect was closed. Postoperatively she had multiple episodes of acute respiratory insufficiency and stridor characterized by marked retention of carbon dioxide. This necessitated reintubation and eventually tracheostomy when laryngeal edema reduced the diameter of the endotracheal tube to 2.5 mm. Lateral chest fluoroscopy revealed almost total expiratory collapse of the distal trachea with diffuse air-trapping. Bronchoscopy confirmed localized expiratory narrowing in the distal trachea. Even with continuous positive airway pressure, she often become cyanotic and lost consciousness when crying or straining.

Two months following repair of the ventricular septal defect, an external rib stent was placed over the malacic trachea through a right thoracotomy. The postoperative course was complicated by persistent laryngeal edema and tracheomalacia at the tracheostomy site. These problems resolved over a two-month period, and the patient was decannulated and discharged from the hospital. Growth and development have been normal during the subsequent nine months. Airway resistances and pressure-flow loops before and after operation are presented in Table 2 and Figure 3.

Table 2. Total Lung Resistances (Atmospheric Minus Intrathoracic Pressures) in Patient 2

Resistances[a] (cm H_2O/L/sec)	Pre-operative	Post-operative	Percent Change
RI	32.6	29.2	1
RE	73.0	35.7	104

[a] Values were calculated at midtidal volume.

RI = inspiratory pulmonary resistance; RE = expiratory pulmonary resistance.

Comment

Previous studies have shown that the trachea in the infant is more compliant than in older children and adults [8, 9, 21]. Bronchoscopy and lateral fluoroscopy show that the distal trachea narrows during expiration [9, 21]. Loss of even small areas of cartilaginous support of the intrathoracic infant trachea may lead to complete collapse during expiration [1, 2, 14]. Data presented here substantiate these clinical observations, documenting markedly abnormal RE in both the piglet tracheomalacia model and the preoperative airway measurements of patients. Maneuvers such as crying, straining, and coughing, which further increase intrathoracic pressure during expiration, accentuate this collapse [8, 18, 21].

The presence of a closed glottis during the early phases of expiration delays narrowing of the airways as intrathoracic pressure increases [18]. In infants with tracheomalacia, the glottic mechanism may reduce the degree of obstruction of the malacic segment by allowing a brief (0.1 to 0.2 sec) [18] increase in intratracheal pressure at the beginning of expiration. When the glottis opens, a bolus of air escapes before the malacic segment collapses. After tracheostomy, loss of the glottis prevents this compensatory mechanism and makes decannulation difficult if not impossible. In our experience, operative treatment of tracheomalacia has been required only in patients with a tracheostomy.

Hyperextension of the neck has been observed in infants with symptomatic tracheomalacia [7, 19]. Data from the piglet model explain this posture. The increase in RE in the flexed, malacic trachea is substantially decreased with hyperextension, particularly at

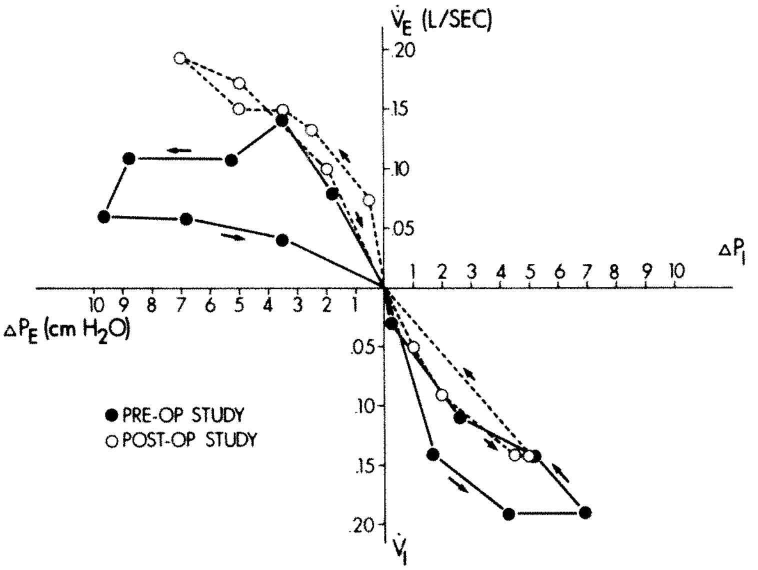

Fig 3. Pressure-flow loops constructed from preoperative and postoperative (two months) data on Patient 2. Each loop is a representative tidal volume plotted to show simultaneous airflow ($\dot{V}$) and pressure differences (ΔP). The slope of a line from the zero point to any point on the loop will give airway resistance at that point. Resistance increases as the line approaches the horizontal axis. (Subscript E = expiratory; subscript I = inspiratory.)

high lung volumes. External stenting of the malacic segment provides longitudinal tension as well as external support across the malacic segment. This longitudinal tension helps to stabilize the malacic segment.

Conservative therapy usually suffices for treatment of tracheomalacia [1, 4, 14]. Temporary endotracheal intubation may be necessary if tracheal edema, inflammation, or acute respiratory failure supervene. A tracheostomy should be avoided but occasionally may be necessary, as in our patients. Although long-term internal stenting has been advocated [10, 13, 17], growth and maturation of the trachea may not result in adequate stabilization of the malacic segment. Our first patient was treated by a tracheostomy stent for four years five months without success.

Tracheal resection has rarely been successful in infants. Our singular experience in an 8-month-old infant resulted in a partial stricture at the anastomotic site. Experimental tracheal resection in puppies has revealed a high incidence of stricture formation, particularly when multiple tracheal segments are removed [15].

Pexis operations have been performed in infants with tracheoesophageal fistulas [2] and anomalous innominate or left carotid arteries [11]. This procedure will support the malacic trachea only if the connective tissue between the artery and the trachea is not disrupted. When vascular compression of the trachea is suspected, however, it often is necessary to fully mobilize trachea and vascular structures so that an unsuspected anomaly is not overlooked.

Nissen [16] and Herzog and colleagues [12] used a free rib graft to stent the adult trachea. In 1968, Vasko and Changwoo [20] described its use in an infant. Our experience shows that the external stent, by supporting and extending the malacic segment, can return the expiratory flow characteristics of the trachea toward normal and substantially reduce R_E. The operation is not difficult to perform and preserves the integrity of the tracheal mucosa.

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Discussion

DR. HERMES C. GRILLO (Boston, MA): This is not completely a reflex response to the appearance of the word *trachea*, for the authors did send me a copy of the manuscript. Their paper deals with a very difficult problem, namely, tracheomalacia in children. They have gone a step further and dealt with basic principles, neatly worked out in experimental studies.

Dr. Johnston stated the basic principles of clinical management: removal of the compressive mass and establishment of the integrity of the airway. There are two variants of tracheomalacia, the type due to external compression, accompanied by softening of the cartilaginous rings, and the type in which the rings are destroyed, often by internal compression, as by tracheostomy tube cuffs.

There are several ways of approaching malacia surgically. When the rings are still present but softened and malacic, even after removal of the compressive mass, as in huge goiters, internal or external splinting may be used. As Dr. Johnston indicated, a Montgomery T-tube may be used until the rings stiffen. I have used buried plastic rings externally in adults in such cases. The Austrians and Swiss have described the use of traction sutures from the tracheal wall tied over "buttons."

When the rings are destroyed the problem is even more difficult. The principal possibilities are external stenting or resection. I am not talking about palliation but about a corrective procedure. I have used both approaches in adults—resection when the segment is relatively easily managed because this is such a safe method, and external stenting occasionally when resection and reconstruction would have been a major problem.

When tiny children are the patients, the problems are special. These problems are edema in a narrow airway and susceptibility to sutureline tension. I think the technique just described by Dr. Johnston is appropriate. The authors deserve congratulations on their results.

DR. HAROLD C. URSCHEL, JR. (Dallas, TX): Following the lead of Dr. Rainer and actually learning from him for fourteen years about the Nissen approach for secondary tracheomalacia in adults, we have operated on approximately 17 patients using the technique of Dr. Rainer who modified the Nissen technique.

Tracheal collapse can develop secondary to chronic obstructive lung disease and is detected on the spirogram by a flat cutoff during the expiratory phase. We operate with the patient in the prone position. A Marlex splint is sewn on the membranous part of the trachea in such a fashion that it acts as a bowstring—across the soft cartilaginous ring.

We have had 1 operative death and about 50% of the patients improved noticeably, 25% improved not at all, and 25% were somewhere between these two groups.

I compliment Dr. Johnston and Dr. Edmunds on these basic contributions to our physiological understanding.

Cold Blood–Potassium Cardioplegia

Leon Levinsky, M.B., B.S., Arthur B. Lee, Jr., M.D., Kee C. Lee, M.D.,
Frank Tatransky, C.C.P., Ronald Dockstader, and George Schimert, M.D.

ABSTRACT **A technique is described for providing myocardial protection utilizing oxygenated blood that is drawn from the pump oxygenator and passed through two disposable cardioplegic cooling coils, which are joined in series and submerged in ice slush. A potassium-containing cardioplegic solution is run into the oxygenated blood at the level of the cooling coils. The amount of blood used in the blood–potassium cardioplegic mixture is controlled using a screw clamp. This method has been used with excellent results in 150 consecutive patients undergoing aortocoronary saphenous vein bypass grafting.**

Hypothermic potassium cardioplegia has been generally adopted as the preferred method to protect the myocardium during open-heart surgery [2, 4]. The potassium in the cardioplegic solution serves to stop the heart rapidly before its metabolic stores are depleted, while hypothermia reduces the energy requirements of the heart during anoxia [2].

During asanguineous cardioplegia, myocardial viability depends upon the energy produced by anaerobic metabolism [3]. However, Bretschneider and associates [1] have emphasized the importance of maintaining aerobic metabolism during pharmacological arrest of the heart. In experimental and clinical studies, Follette and co-workers [3] showed that blood cardioplegia offers better myocardial protection and operating conditions than intermittent ischemia or continuous coronary perfusion. During the past year we have changed to a simple system of blood cardioplegia.

The Perfusion System

The components of the perfusion system are illustrated in the Figure. A Y-connector is inserted into the arterial line distal to the arterial pump. This carries blood to cardioplegic solution heat-exchanging coils (Cobe Company) connected in series and immersed in a basin of ice slush; the blood passes through two coils because it must be cooled from 30° to 8°C. The cardioplegic solution is made up of the following:

Potassium chloride	26 mEq/L
Glucose	43.9 gm/L
Mannitol	12.5 gm/L
Sodium bicarbonate	2.67 mEq/L
Solu-Medrol (methylprednisolone sodium succinate)	1 gm/L
Vehicle	Normosol-R (Abbott)
pH	7.60
Osmolality	480 mOsm/Kg H_2O

The potassium cardioplegic solution, which is precooled, passes through a filter and bubble trap and then through a Y-connector into the second of the two cardioplegic solution coils. A Sarns low-flow perfusion pump is used to administer the cardioplegic solution. The blood-cardioplegia mixture is instilled through a U.S.C.I. 10F catheter with six side-holes that is inserted through a pursestring suture in the aortic root.

The blood-cardioplegia system is debubbled before bypass is commenced. Blood flow is controlled by a screw clamp situated just proximal to the U.S.C.I. catheter, and the flow of cardioplegic solution is regulated by adjusting the Sarns low-flow perfusion pump.

Method of Producing Cardioplegia

Before the U.S.C.I. cannula is inserted into the ascending aorta, the screw clamp is adjusted to

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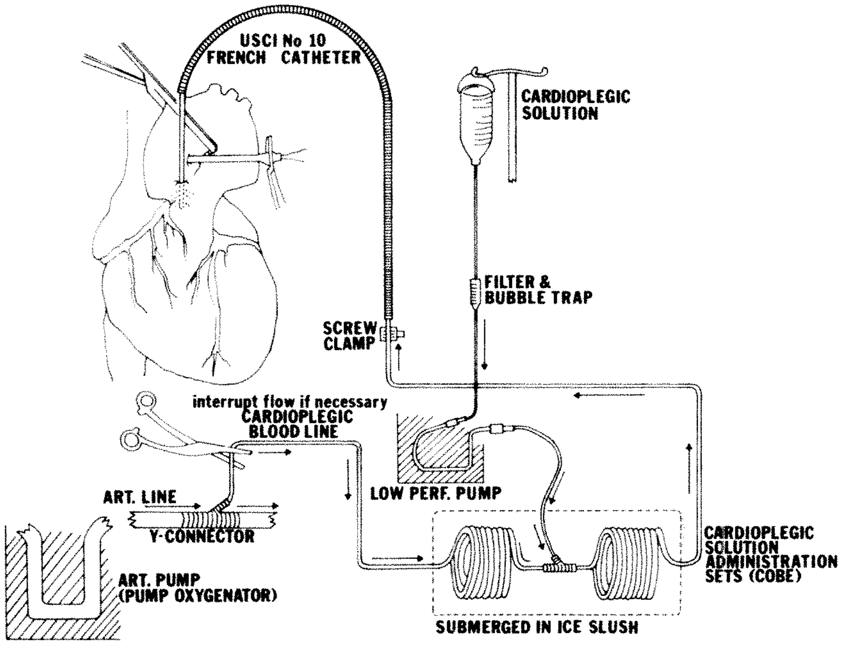

The cold blood–potassium cardioplegia system.

allow a blood flow of 120 ml per minute. This is done either by timing the blood flow into a measured beaker or by using a flow probe. The blood line is then clamped, the aorta is cross-clamped, and the U.S.C.I. cannula is inserted into the ascending aorta. The potassium cardioplegic solution is initially administered alone in order to produce swift arrest of the heart; usually 400 to 600 ml of cardioplegic solution suffices. Once the heart has arrested, the clamp is removed from the blood line and cold blood is administered at a rate of 120 ml per minute. The potassium cardioplegic solution is run at a rate of 10 to 20 ml per minute. The initial temperature of the cold blood–potassium cardioplegia solution as it leaves the U.S.C.I. catheter is 6° to 8°C. Topical hypothermia is also used, and the myocardial temperature, monitored with a temperature probe, is kept between 8° and 10°C throughout the period of anoxia. Because of the large volume of blood infused through the coronary arteries, the superior and inferior venae cavae are not snared, and the left side of the heart must be decompressed by venting.

The flow of blood in the coronary arteries is sometimes troublesome while the distal anastomoses are being performed, and the blood line may then be temporarily clamped. Similarly, if the heart shows any signs of contraction, the blood line may be clamped and an extra boost of cardioplegic solution may be given.

Pressure in the ascending aorta measures from 20 to 30 mm Hg while the cold blood–potassium cardioplegic solution is being administered, and rises to 50 to 70 mm Hg when the heart is displaced upward for anastomosis of marginal circumflex vessels.

All of the blood–potassium cardioplegia solution is returned to the pump oxygenator. However, a high concentration of potassium is only intermittently infused. When the potassium cardioplegic solution is instilled together with the cold blood, potassium is diluted to a concentration of 8 to 10 mEq per liter. Diuretics are used to maintain high diuresis during the procedure, and there has been no problem with hyperkalemia or with excessive hemodilution of the pump oxygenator perfusate, which is kept at a hematocrit of between 22 and 26%. There is a potential danger of raising the potassium concentration of the perfusate to high levels if much greater volumes of cardioplegic solution than those described are used.

Results and Conclusion

This method of myocardial protection using cold blood with potassium cardioplegia has been used in 150 consecutive unselected patients undergoing coronary artery bypass grafting. The aortic cross-clamp time ranged from 40 to 140 minutes (mean, 92 ± 11.1). There were no hospital deaths. Two patients required intraaortic balloon assistance and 8 needed inotropic drugs in the pump weaning period. Perioperative infarction was documented in 4 patients (2.7%) according to electrocardiographic and creatine phosphokinase isoenzyme criteria.

The method described here permits selective use of potassium cardioplegic solution to arrest the heart or whenever mechanical activity is evident. When the cold blood is being infused, potassium is diluted to a concentration of 8 to 10 mEq per liter; a high concentration of potassium is therefore only intermittently instilled. The heart is kept consistently cold (8° to 10°C) with this method. The postoperative course of patients treated with blood-cardioplegia appears quite benign, and we now prefer to use this method in all open-heart surgical procedures.

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CLASSICS IN THORACIC SURGERY

Correction of Aortic Coarctation

Clarence Crafoord, M.D.

Dr. Clarence Crafoord

ABSTRACT **Experiments performed in the 1930s demonstrated the results of cross-clamping the aorta in animals. Findings from these experiments permitted cross-clamping of the aorta both above and below the origin of the ductus, in a series of ductus Botalli cases. This experience in turn led to the decision to perform a radical operation for coarctation of the aorta by placing clamps above and below the coarctation, removing the clamps, and sewing the aorta end-to-end. The first coarctation resection was performed on October 19, 1944.**

A total of 216 operations for aortic coarctation were performed from 1944 to January, 1958. In the last 180 patients, use of a continuous, everting end-to-end suture practically excluded complications from the suture. With this technique there were few complications and a primary mortality not exceeding 6%.

This is a brief retrospective report of the sequence of events that led to my decision to perform aortic resection and end-to-end sutures in the repair of coarctation of the aorta.

Background

Methods were gradually developed whereby the patient's spontaneous breathing could be taken over by artificial volume- or pressure-controlled respiration within normal respiratory-physiological limits, under simultaneous general anesthesia, through airtight connections to the trachea. Conditions were then created for wide open unilateral and bilateral intrathoracic operations more or less without a time limit.

Results of Experimental Studies

The aim of experimental studies during the early 1930s was to prolong the duration for surgical removal of obturating lung emboli. In 1927 I had performed two such operations successfully despite the restricted time then available. My intention was to prolong these time periods without allowing such a lack of oxygen in the organs, particularly in the brain, that resumption of normal functions became impossible. During these experiments I learned, among other things, the results both of clamping different big vessels within the thoracic cavity examined and of cross-clamping the aorta, both centrally near the heart and more peripherally after the origin of the major vessels to different parts of the body. Such aortic clampings were performed with and without artificial brain circulation. This circulation in the experimental animal was made possible by connecting the central carotid arteries and internal jugular veins of one animal with the peripheral ends of the same arteries and veins of the animal undergoing aortic cross-clamping. Both animals were of the same species and were lying beside one another for the experiment.

Ductus Botalli Operations

Thanks to the results of these various aortic cross-clampings on experimental animals, I dared, in the beginning of my series of patients

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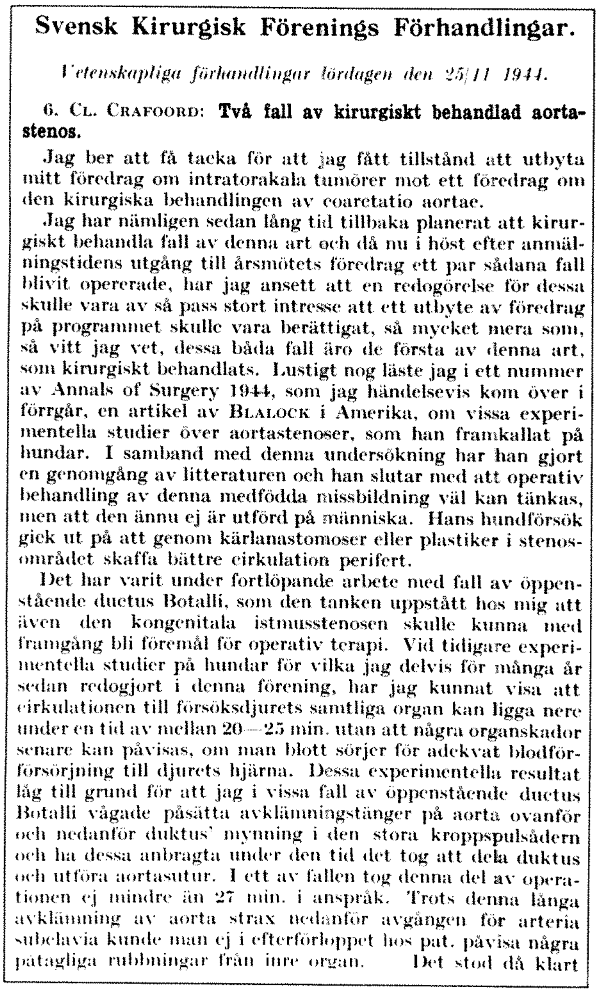
with ductus Botalli, to cross-clamp the aorta both above and below the origin of the ductus for periods of a few minutes. This was done to enable me to place aortic sutures calmly after division of the ductus Botalli, which I believed was better and safer in many cases than just ligating the ductus. Because of complications during this phase of the operation in a patient with a very wide ductus, in whom the aortic wall was thin and fragile, the aortic cross-clamping lasted almost 17 minutes. No circulatory disturbances resulted to other organs.

First Coarctation Resection

My experience led me to consider the possibilities of radical operation for coarctation of the aorta by placing clamps above and below



Svensk Kirurgisk Förenings Förhandlingar.

Vetenskapliga förhandlingar lördagen den 25/11 1944.

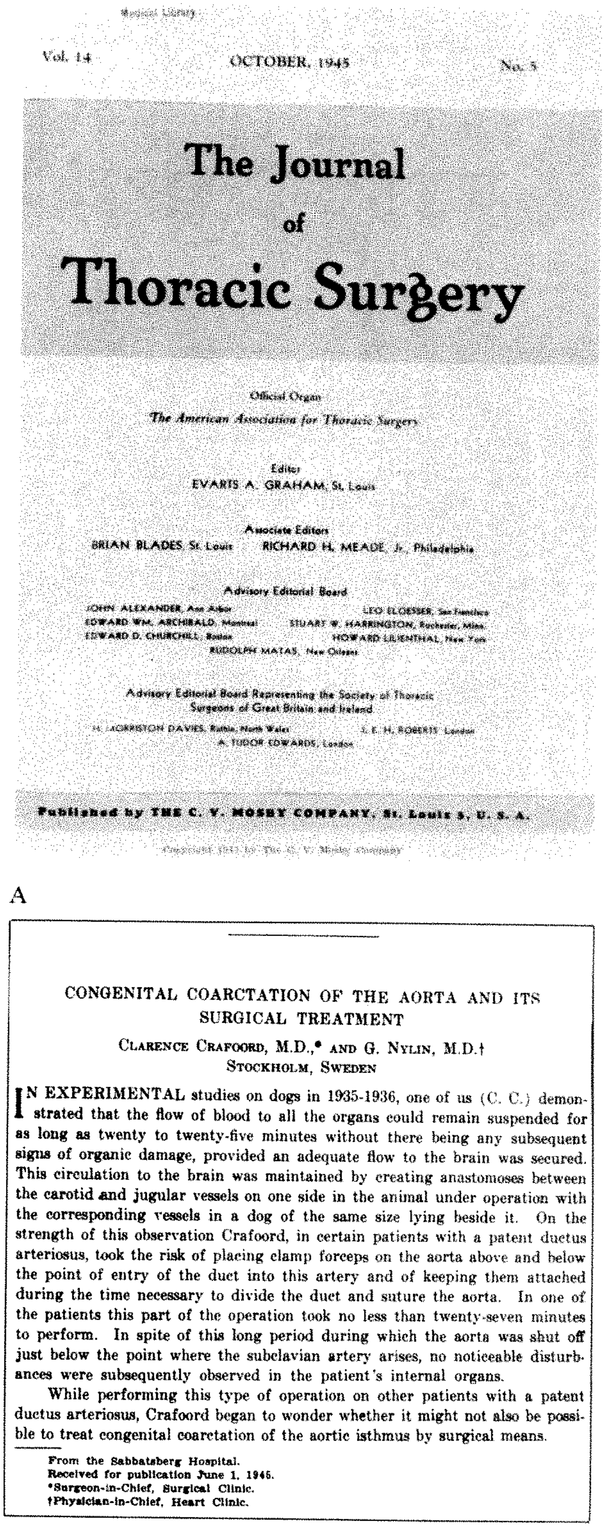
6. Cl. Crafoord: **Två fall av kirurgiskt behandlad aortastenos.**

Jag ber att få tacka för att jag fått tillstånd att utbyta mitt föredrag om intratorakala tumörer mot ett föredrag om den kirurgiska behandlingen av coarctatio aortae.

Jag har nämligen sedan lång tid tillbaka planerat att kirurgiskt behandla fall av denna art och då nu i höst efter anmälningstidens utgång till årsmötets föredrag ett par sådana fall blivit opererade, har jag ansett att en redogörelse för dessa skulle vara av så pass stort intresse att ett utbyte av föredrag på programmet skulle vara berättigat, så mycket mera som, så vitt jag vet, dessa båda fall äro de första av denna art, som kirurgiskt behandlats. Lustigt nog läste jag i ett nummer av Annals of Surgery 1944, som jag händelsevis kom över i förrgår, en artikel av Blalock i Amerika, om vissa experimentella studier över aortastenoser, som han framkallat på hundar. I samband med denna undersökning har han gjort en genomgång av litteraturen och han slutar med att operativ behandling av denna medfödda missbildning väl kan tänkas, men att den ännu ej är utförd på människa. Hans hundförsök gick ut på att genom kärlanastomoser eller plastiker i stenosområdet skaffa bättre cirkulation perifert.

Det har varit under fortlöpande arbete med fall av öppenstående ductus Botalli, som den tanken uppstått hos mig att även den kongenitala istmusstenosen skulle kunna med framgång bli föremål för operativ terapi. Vid tidigare experimentella studier på hundar för vilka jag delvis för många år sedan redogjort i denna förening, har jag kunnat visa att cirkulationen till försöksdjurets samtliga organ kan ligga nere under en tid av mellan 20—25 min. utan att några organskador senare kan påvisas, om man blott sörjer för adekvat blodförförsörjning till djurets hjärna. Dessa experimentella resultat låg till grund för att jag i vissa fall av öppenstående ductus Botalli vågade påsätta avklämningstänger på aorta ovanför och nedanför duktus' mynning i den stora kroppspulsådern och ha dessa anbragta under den tid det tog att dela duktus och utföra aortasutur. I ett av fallen tog denna del av operationen ej mindre än 27 min. i anspråk. Trots denna långa avklämning av aorta strax nedanför avgången för arteria subclavia kunde man ej i efterförloppet hos pat. påvisa några påtagliga rubbningar från inre organ. Det stod då klart

Fig 1. *Report of the first coarctation repairs to the Swedish Surgical Association, Nov 11, 1944. (Reproduced from Nordisk Medicine 26:864, 1945, with permission from the publisher.)*



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A

CONGENITAL COARCTATION OF THE AORTA AND ITS SURGICAL TREATMENT

Clarence Crafoord, M.D.,* and G. Nylin, M.D.†
Stockholm, Sweden

In EXPERIMENTAL studies on dogs in 1935-1936, one of us (C. C.) demonstrated that the flow of blood to all the organs could remain suspended for as long as twenty to twenty-five minutes without there being any subsequent signs of organic damage, provided an adequate flow to the brain was secured. This circulation to the brain was maintained by creating anastomoses between the carotid and jugular vessels on one side in the animal under operation with the corresponding vessels in a dog of the same size lying beside it. On the strength of this observation Crafoord, in certain patients with a patent ductus arteriosus, took the risk of placing clamp forceps on the aorta above and below the point of entry of the duct into this artery and of keeping them attached during the time necessary to divide the duct and suture the aorta. In one of the patients this part of the operation took no less than twenty-seven minutes to perform. In spite of this long period during which the aorta was shut off just below the point where the subclavian artery arises, no noticeable disturbances were subsequently observed in the patient's internal organs.

While performing this type of operation on other patients with a patent ductus arteriosus, Crafoord began to wonder whether it might not also be possible to treat congenital coarctation of the aortic isthmus by surgical means.

From the Sabbatsberg Hospital.
Received for publication June 1, 1945.
*Surgeon-in-Chief, Surgical Clinic.
†Physician-in-Chief, Heart Clinic.

B

Fig 2. *(A) Front page of the October, 1945, issue of The Journal of Thoracic Surgery in which the first coarctation repairs were reported in the English literature. (B) Title page of that article. (From Crafoord C, Nylin G: Congenital coarctation of the aorta and its surgical treatment. J Thorac Surg 14:Cover, 347, 1945.)*

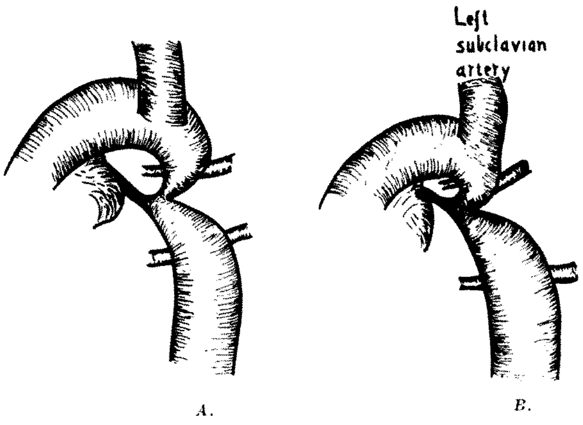

Fig. 14.—A, Case 1; B, Case 2.

Fig 3. There is conical narrowing of the aorta from the origin of the subclavian artery to the coarctation. This is much longer in the first patient, a small boy (Case 1), than in the second (Case 2). (From Crafoord C, Nylin G: Congenital coarctation of the aorta and its surgical treatment. J Thorac Surg 14:358, 1945.)

the coarctation and then removing the latter and sewing the aorta end-to-end. The aortic cross-clamping time would thus be more or less unlimited due to the rich net of collaterals between the arteries above and below the coarctation. These are the reasons why I decided in 1943 to perform a coarctation resection. The decision, however, was not put into effect until October 19, 1944, because no patients were referred to me or my cardiologist colleagues for diagnosis (Figs 1–3).

In my lecture to the American College of Surgeons on July 5, 1958, I reported my series of 216 patients who had undergone coarctation resection to January, 1958. In the first 36 patients, I used what I call an anatomical continuous over-and-over suture with a few added isolated sutures so that the different layers of the aortic wall were firmly approximated to each other. However, in this small series there was an unduly high frequency of complications because of insufficiency of the suture line. In the remaining 180 patients, I used a continuous, end-to-end everting suture sometimes reinforced with a few isolated everting sutures. This method practically excluded complications from the suture line. Only in isolated cases in which either preoperatively or at exploratory thoracotomy it was considered impossible to resect and suture end-to-end, were grafts contemplated and even used during my active time as surgeon.

With the described technique, I have experienced very few complications and a primary mortality not exceeding 6%. One important fact that I have learned from my series of coarctation resections is that these lesions are much more often combined with other congenital and acquired heart malformations on the big vessels close to the heart than I realized at first. Therefore, all available diagnostic means must be used in order to exclude such complications, and if they are present, they must be taken into consideration when the indications for operation are evaluated. If possible, these lesions should be operated on simultaneously or in stages if necessary.

Enlargement of Aortic Root

To the Editor:

I am writing in regard to the article entitled "Radical Enlargement of the Aortic Root and Outflow Tract to Allow Valve Replacement" (Ann Thorac Surg 27:367, 1979) by Rittenhouse and associates.

I would like to inform you that at the Department of Thoracic and Cardiovascular Surgery of Göttingen University in September, 1974, I began the experimental development of radical enlargement of the aortic root and left ventricular outflow tract by incising the aortic annulus, the aortic leaflet of the mitral valve, and the superior aspect of the left atrium. Following reconstruction of the resulting defects, the aortic valve was replaced by a suitable, larger prosthesis. Between November, 1975, and April, 1979, 16 patients underwent this surgical procedure, which I described first in February, 1976.

For your information, I send you our bibliography regarding this surgical procedure.

Priv. Doz. Dr. S. Manouguian

Chirurg. Abt. des Kreiskrankenhauses Northeim, Sturmbäume 8, 3410 Northeim, West Germany

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PROGRAM
FOR THE TWENTY-SEVENTH ANNUAL MEETING OF THE SOUTHERN THORACIC SURGICAL ASSOCIATION APPROVED FOR CATEGORY I CME CREDIT (14 Hr)

November 13–15, 1980
The Greenbrier, White Sulphur Springs, WV

November 13, 1980 (Thursday)
Postgraduate Program

Selected Operations by Experts
Moderator: Maruf A. Razzuk, M.D., Dallas, TX

8:30 1. Resection of Superior Sulcus Tumor
Donald Paulson, M.D., Dallas, TX

2. Technique of Bronchoplasty
Harold C. Urschel, Jr., M.D., Dallas, TX

3. Repair of Pectus Excavatum and Pectus Carinatum
Francis Robicsek, M.D., Charlotte, NC

4. Esophageal Substitute (Colonic, Jejunal, and Gastric Tubes)
J. Alex Haller, Jr., M.D., Baltimore, MD

5. Esophagogastrectomy
Joseph Peabody, M.D., Washington, DC

6. Panel Discussion

Break

10:30 7. Myocardial Protection
Dennis F. Pupello, M.D., Tampa, FL

8. Double-Valve Replacement
Charles R. Hatcher, Jr., M.D., Atlanta, GA

9. Resection of Arch Aneurysm
Stanley Crawford, M.D., Houston, TX

10. Treatment of Dissecting Thoracic Aneurysm (Medical and Surgical)
Myron Wheat, M.D., St. Petersburg, FL

11. Panel Discussion

November 13, 1980 (Thursday)
Afternoon Scientific Session

1:30 1. High-Output Failure following Cardiopulmonary Bypass
Andrew S. Wechsler, M.D., Kenneth Hall, M.D., Hans Karis, M.D., and W. Glenn Young, Jr., M.D., Durham, NC

2. Clinical Experience with Preoperative Myocardial Nutrition Management
David M. Lolley, M.D., Madisonville, KY, Jefferson F. Ray, III, M.D., William O. Myers, M.D., Richard D. Sautter, M.D., and Duane A. Tewksbury, M.D., Marshfield, WI, Harold C. Urschel, Jr., M.D., and Maruf A. Razzuk, M.D., Dallas, TX

3. Coronary Bypass for Relief of Persistent Pain following Acute Myocardial Infarction
Ellis Jones, M.D., Thad F. Waites, M.D., Joe M. Craver, M.D., James M. Bradford, M.D., Spencer B. King, M.D., John S. Douglas, M.D., Edward R. Dorney, M.D., Stephen D. Clements, M.D., and Charles R. Hatcher, Jr., M.D., Atlanta, GA

4. Early Operative Intervention in Aortic Bacterial Endocarditis
Richard L. Prager, M.D., Michael D. Maples, M.D., John W. Hammon, Jr., M.D., Gottlieb C. Friesinger, M.D., and Harvey W. Bender, Jr., M.D., Nashville, TN

5. Clinical Evaluation for the 19 mm Björk-Shiley Aortic Valve Prosthesis
   Hartzell V. Schaff, M.D., Robert K. Brawley, M.D., Clifford Hughes, M.D., Stephen Achuff, M.D., Timothy J. Gardner, M.D., James S. Donahoo, M.D., and Vincent L. Gott, M.D., Baltimore, MD

   Break

3:30 6. Alterations in Pulmonary Function after Pneumonectomy for Bronchogenic Carcinoma
   Edward J. Dunn, M.D., Jose Hernandez, M.D., Harvey W. Bender, Jr., M.D., and Richard L. Prager, M.D., Nashville, TN

7. Complication of Intrathoracic Nissen Fundoplication
   Kamal A. Mansour, M.D., and Joseph I. Miller, M.D., Atlanta, GA

8. An Analysis of the Isoenzymes of Creatine Phosphokinase and Lactic Dehydrogenase in the Esophagus
   Geoffrey M. Graeber, M.D., Michael J. Reardon, Ph.D., Arthur W. Fleming, M.D., Harold D. Head, M.D., Rostik Zajtchuk, M.D., Walter H. Brott, M.D., and John H. Foster, M.D., Bethesda, MD

9. The Extended (Congenital) Type of Barrett's Esophagus in the Adult
   John M. Ransom, M.D., Ganesh K. Patel, M.D., and Raymond C. Read, M.D., Little Rock, AR

10. Cardiovascular Surgery at the King Faisal Specialist Hospital in Riyadh, Saudi Arabia: Two-Year Experience
   Kenneth L. Mattox, M.D., Arthur C. Beall, Jr., M.D., Gene Quinn, M.D., Nizar Feteih, M.D., Gerald M. Lawrie, M.D., Hartwell H. Whisennand, M.D., Mohammed Mardini, M.D., and Michael E. DeBakey, M.D., Houston, TX

November 14, 1980 (Friday)
Morning Scientific Session

8:30 11. Management of Patients with Delayed Tamponade following Open-Heart Operation
   A. Michael Borkon, M.D., Hartzell V. Schaff, M.D., Timothy J. Gardner, M.D., Robert K. Brawley, M.D., James S. Donahoo, M.D., and Vincent L. Gott, M.D., Baltimore, MD

12. Continuous Hydralazine Infusion for Afterload Reduction
   Mark J. Swartz, B.A., George C. Kaiser, M.D., Vallee L. Willman, M.D., John E. Codd, M.D., Denis H. Tyras, M.D., and Hendrick B. Barner, M.D., St. Louis, MO

13. Use of Cold Cardioplegic Solution for Vein Graft Distention and Preservation: A Light and Scanning Electron Microscopic Study
   E. H. Williams, M.D., M. A. Kurusz, M.D., E. W. Christman, M.D., J. R. Derrick, M.D., and G. F. O. Tyers, M.D., Galveston, TX

14. Hemodynamic and Scintigraphic Measures of Ventricular Function and Compliance Immediately after Cardiac Operation
   Charles H. Moore, M.D., James A. Allums, M.D., and Fallon T. Gordon, M.D., Beaumont, TX

15. Clinical and Experimental Evaluation of Left Ventriculoiliac Shunt Bypass during Repair of Lesions of the Descending Thoracic Aorta
   Paul T. Frantz, M.D., John A. Shallal, M.D., and Gordon F. Murray, M.D., Chapel Hill, NC

   Break

10:30 Presidential Address: A Southern Surgeon—and Gentleman
W. Glenn Young, Jr., M.D., Durham, NC

11:30 Business Meeting (members only)

November 15, 1980 (Saturday)
Morning Scientific Session

8:30 16. Management of Thoracic Empyema
Norman Snow, M.D., Aaron Lucas, M.D., and Laman A. Gray, Jr., M.D., Louisville, KY

17. The Management of Nontraumatic Chylothorax
John L. Strausser, M.D., and M. Wayne Flye, M.D., Bethesda, MD

18. Middle Lobe Syndrome: Diagnosis and Management
Sibu P. Saha, M.D., Porter Mayo, M.D., and Graydon A. Long, M.D., Lexington, KY, and Richard B. McElvein, M.D., Birmingham, AL

19. Thoracoscopy for Intrathoracic Tumors
B. M. Rodgers, M.D., F. C. Ryckman, M.D., F. Moazam, M.D., and J. L. Talbert, M.D., Gainesville, FL

20. Pulmonary Embolectomy
David M. Glassford, Jr., M.D., William S. Stoney, M.D., William C. Alford, Jr., M.D., George R. Burrus, M.D., and Clarence S. Thomas, Jr., M.D., Nashville, TN

Break

10:30 21. Correction of Left Atrial Abnormalities in Children by the Superior Approach
A. A. Richi, M.D., R. M. Sade, M.D., M. G. May, M.D., and A. R. Hohn, M.D., Charleston, SC

22. The Role of Proximal Subclavian Stenosis in Coronary Artery Revascularization
William H. Edwards, M.D., and Joseph L. Mulherin, Jr., M.D., Nashville, TN

23. Glenn Shunt: Current Role in Congenital Heart Operations
D. G. Pennington, M.D., and S. Nouri-Maghaddam, St. Louis, MO

24. The Embolization of Bone Wax from Sternotomy Incisions
Francis Robicsek, M.D., Thomas N. Masters, Ph.D., Harry K. Daugherty, M.D., Joseph W. Cook, M.D., Jay G. Selle, M.D., and Laszlo Littmann, M.D., Charlotte, NC

25. Severe Bronchospasm at Termination of Cardiopulmonary Bypass: Recognition and Treatment of a Potentially Fatal Complication
G. Lionel Zumbro, M.D., George L. Shearer, C.C.P., Philip W. Catalano, M.D., and Ronald F. Galloway, M.D., Augusta, GA

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Experienced **cardiac and thoracic surgeon,** 41, seeking to relocate. Six years' experience in an active private practice; trained at major midwestern university. ABS, ABTS certified. Will consider all areas. Curriculum vitae upon request.

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Cardiovascular and thoracic surgeon, 35, well trained at major university center, seeks faculty position or association with private group. No geographic preference. Available immediately.

Please respond to W-231, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon, 35, ABS, ABTS Part I, one year of experience in a very busy cardiovascular and thoracic surgery program. Would like to relocate and prefers Southeast, but will consider other locations.

Please respond to W-232, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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Please respond to W-235, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiothoracic surgeon, 34, ABS, ABTS certified, university trained, publications, wishes to relocate. Experience includes adult thoracic and pediatric cardiac surgery.

Please respond to W-237, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon, 34, ABS, ABTS, university trained, presently at major university medical center, wishes to enter private practice or relocate to another teaching program. Experienced in adult and pediatric cardiac, thoracic, and vascular surgery. Will consider all locations. CV and operative experience available upon request.

Please respond to W-238, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiothoracic surgeon, 37, university trained, congenital cardiac surgery fellowship, ABTS certified, extensive bibliography, two years' clinical experience, seeking to relocate. Desires position leading to partnership or opportunity to start new program in adult and/or pediatric cardiac surgery.

Please respond to W-239, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon, 38, university trained, ABS, ABTS certified, desires position in private practice. Currently associate professor in active university program. Extensive experience in cardiac, thoracic, and vascular surgery. Prefers Northeast or upper Midwest. Curriculum vitae upon request.

Please respond to W-240, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

SITUATIONS AVAILABLE

The Chicago Heart and Lung Hospital is under construction at 6500 S Pulaski Rd for the management of cardiovascular and lung diseases exclusively, including open-heart surgery. **Applications are being accepted for Board-certified cardiologists, thoracic and cardiovascular surgeons, and cardiac anesthesiologists.** Apply immediately while there are still openings on the staff.

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Please reply to Cardiovascular Surgery Associates, Suite 501, St. Thomas Medical Building, 4230 Harding Rd, Nashville, TN 37205.

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Board-eligible thoracic surgeon wanted for expanding West Coast group. Adult cardiac, thoracic, and vascular training essential. Starting dates considered up to July 1981.

Please respond to A-208, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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Please respond to A-209, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Board-certified or Board-eligible thoracic surgeon wanted to join well-established practice in rapidly growing city in the Southwest.

Send curriculum vitae to A-210, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 41809, or telephone (602) 881-1163.

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Please respond to A-212, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Thoracic surgeon, Board eligible or certified, **wanted** to join a busy thoracic surgeon in Boston area.

Please respond to A-213, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Thoracic surgical group in suburban Boston **seeks new associate,** ABTS certified or eligible.

Submit resume and curriculum vitae to A-214, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Full-time academic position available for cardio-thoracic surgeon at assistant professor level. Must be university trained, Board eligible or Board certified.

Send curriculum vitae to Sidney Levitsky, M.D., Chief, Division of Cardio-Thoracic Surgery, University of Illinois Medical Center, P.O. Box 6998, Chicago, IL 60680. An equal opportunity/affirmative action employer.

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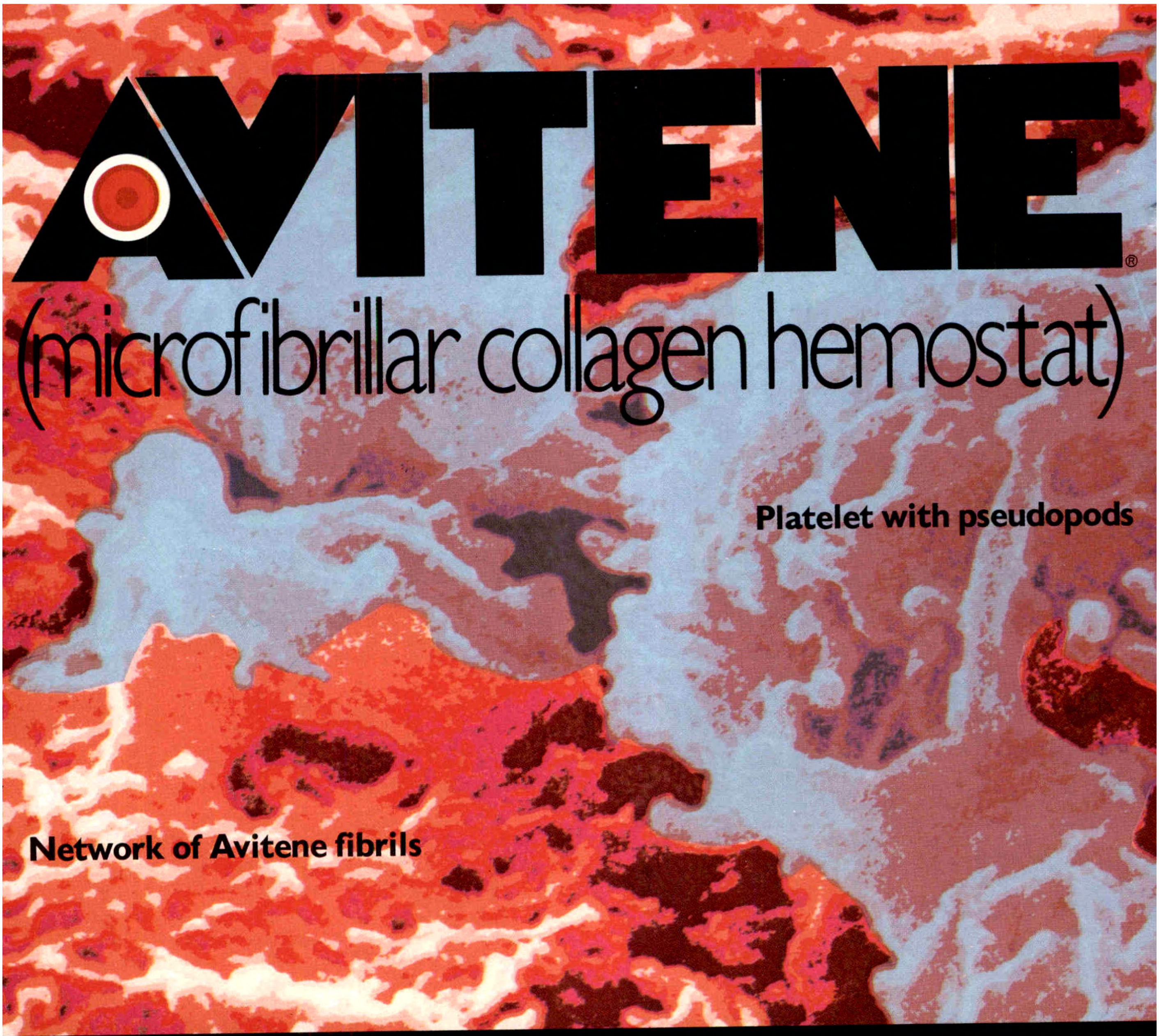

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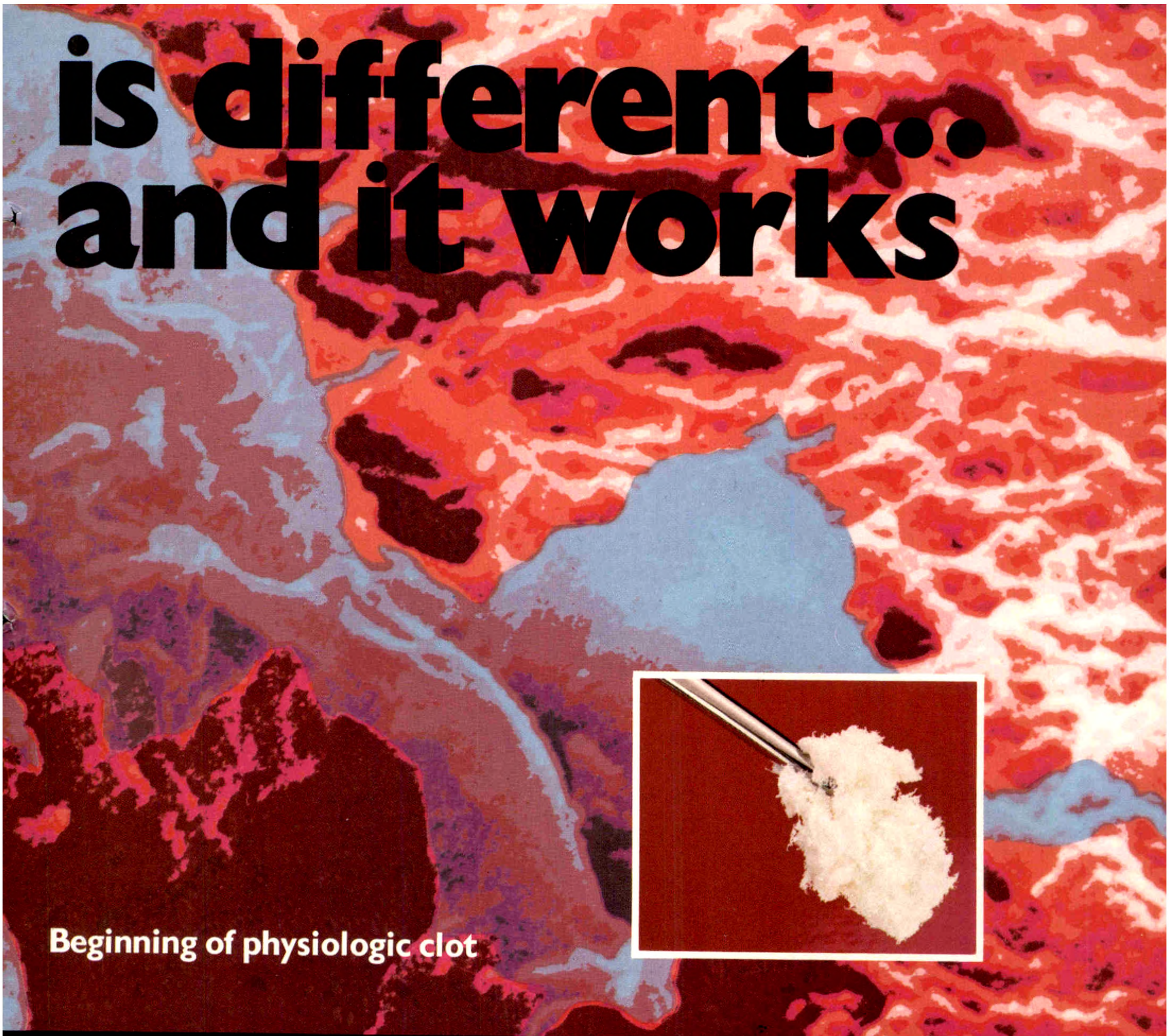

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Warnings: Avitene is inactivated by autoclaving. Ethylene oxide reacts with bound hydrochloric acid to form ethylene chlorohydrin. This product should not be resterilized. It is not for injection. Moistening Avitene or wetting with saline or thrombin impairs its hemostatic efficacy. It should be used *dry*. Discard any unused portion. As with any foreign substance, use in contaminated wounds may enhance infection.

Precautions: Only that amount of Avitene necessary to produce hemostasis should be used. After several minutes, excess material should be removed; this is usually possible without the reinitiation of active bleeding. Failure to remove excess Avitene may result in bowel adhesions or mechanical pressure sufficient to compromise the ureter. In otolaryngological surgery, precautions against aspiration should include removal of all excess dry material and thorough irrigation of the pharynx. Avitene contains a low, but detectable, level of intercalated bovine serum protein which reacts immunologically as does beef serum albumin. Increases in anti-BSA titer have been observed following treatment with Avitene. About two-thirds of individuals exhibit antibody titers because of ingestion of food products of bovine origin. Intradermal skin tests have occasionally shown a weak positive reaction to BSA or Avitene but these have not been correlated with IgG titers to BSA. Tests have failed to demonstrate clinically significant elicitation of antibodies of the IgE class against BSA following Avitene therapy. Care should be exercised to avoid spillage on nonbleeding surfaces, particularly in abdominal or thoracic viscera. Teratology studies in rats and rabbits have revealed no harm to the animal fetus. There are no well-controlled studies in pregnant women; therefore, Avitene should be used in pregnant women only when clearly needed.

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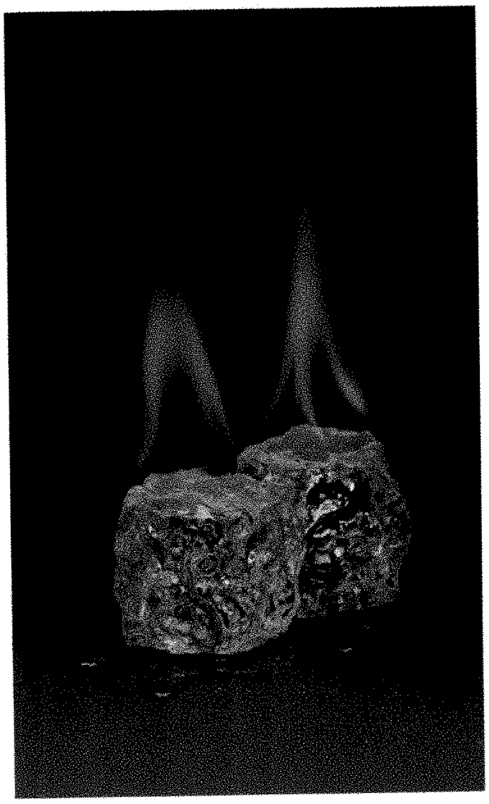

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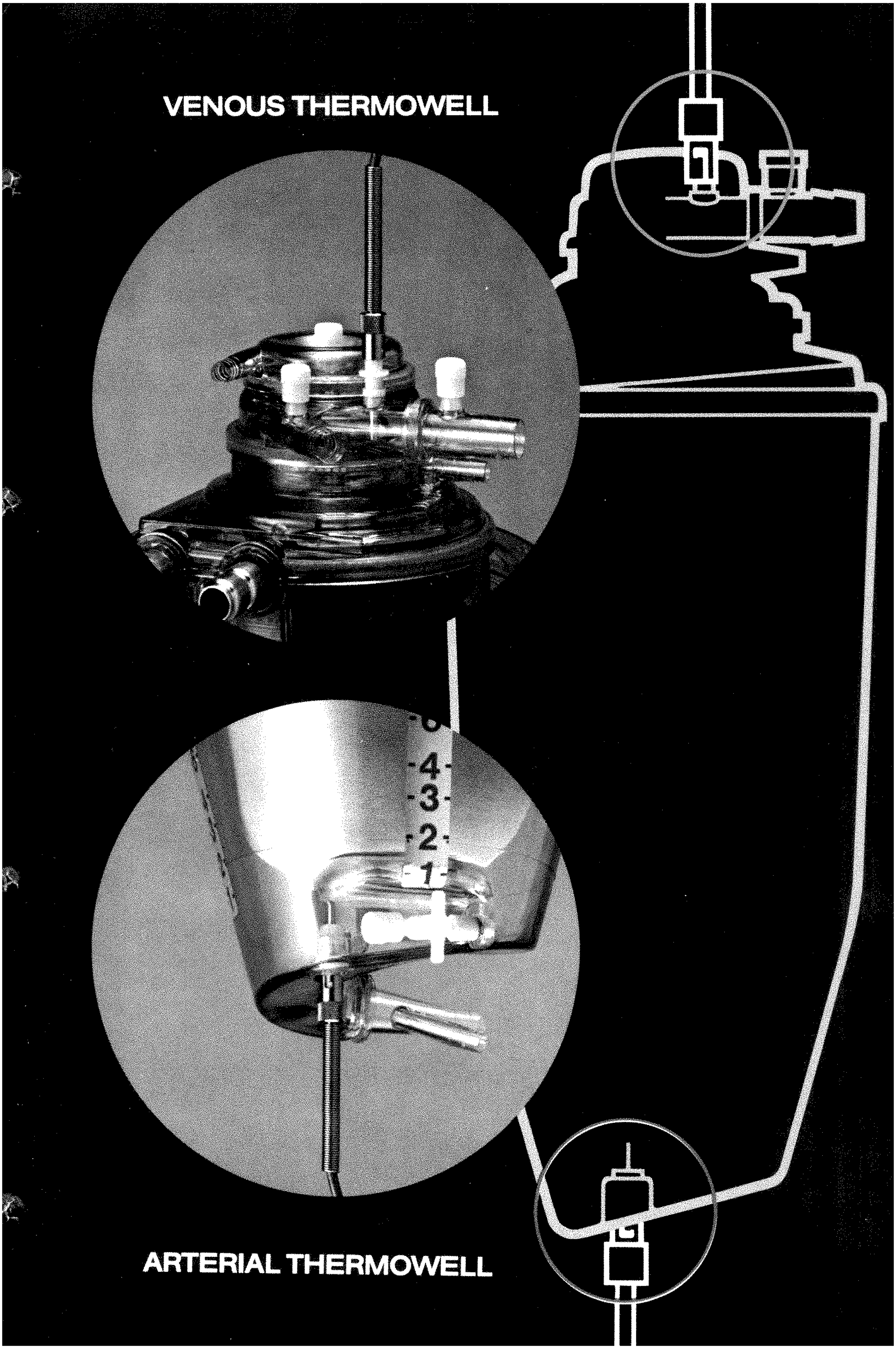
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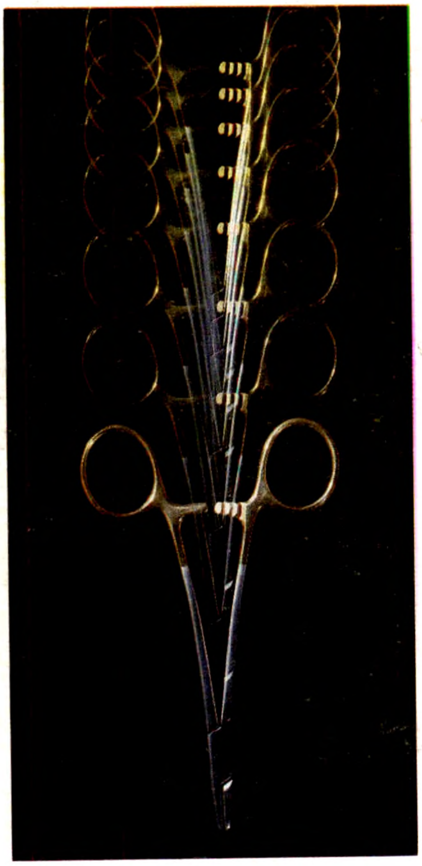

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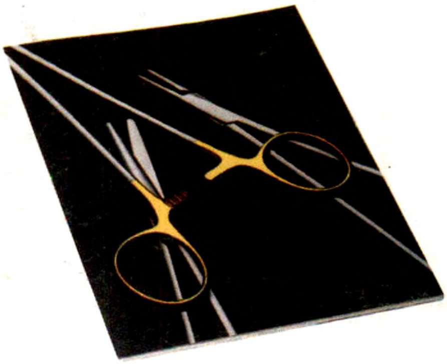

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Volume 30 Number 4 October 1980

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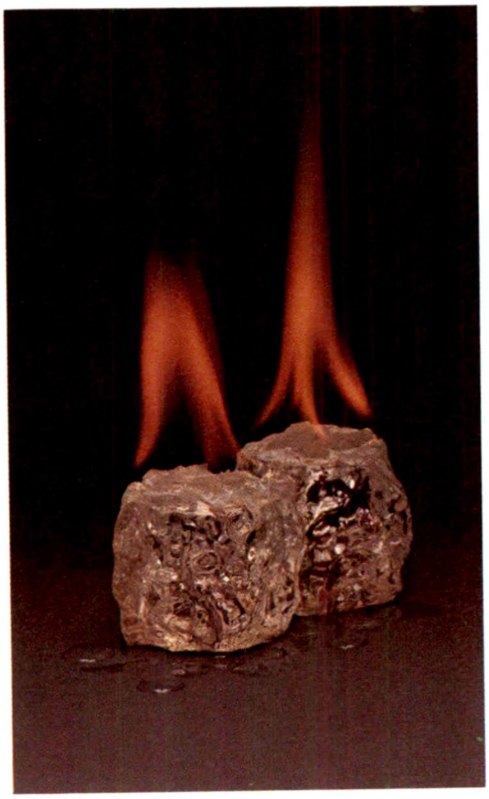

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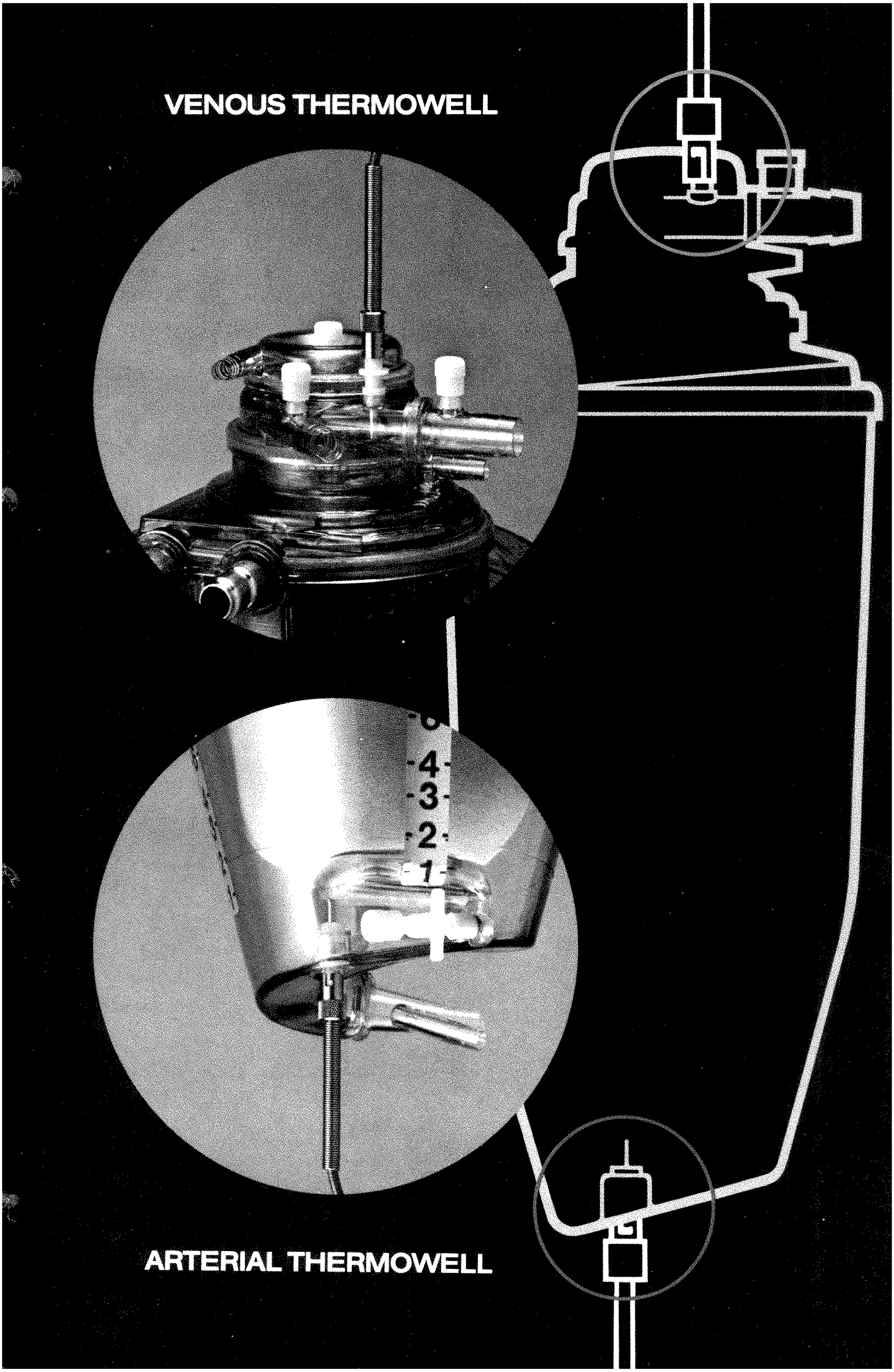
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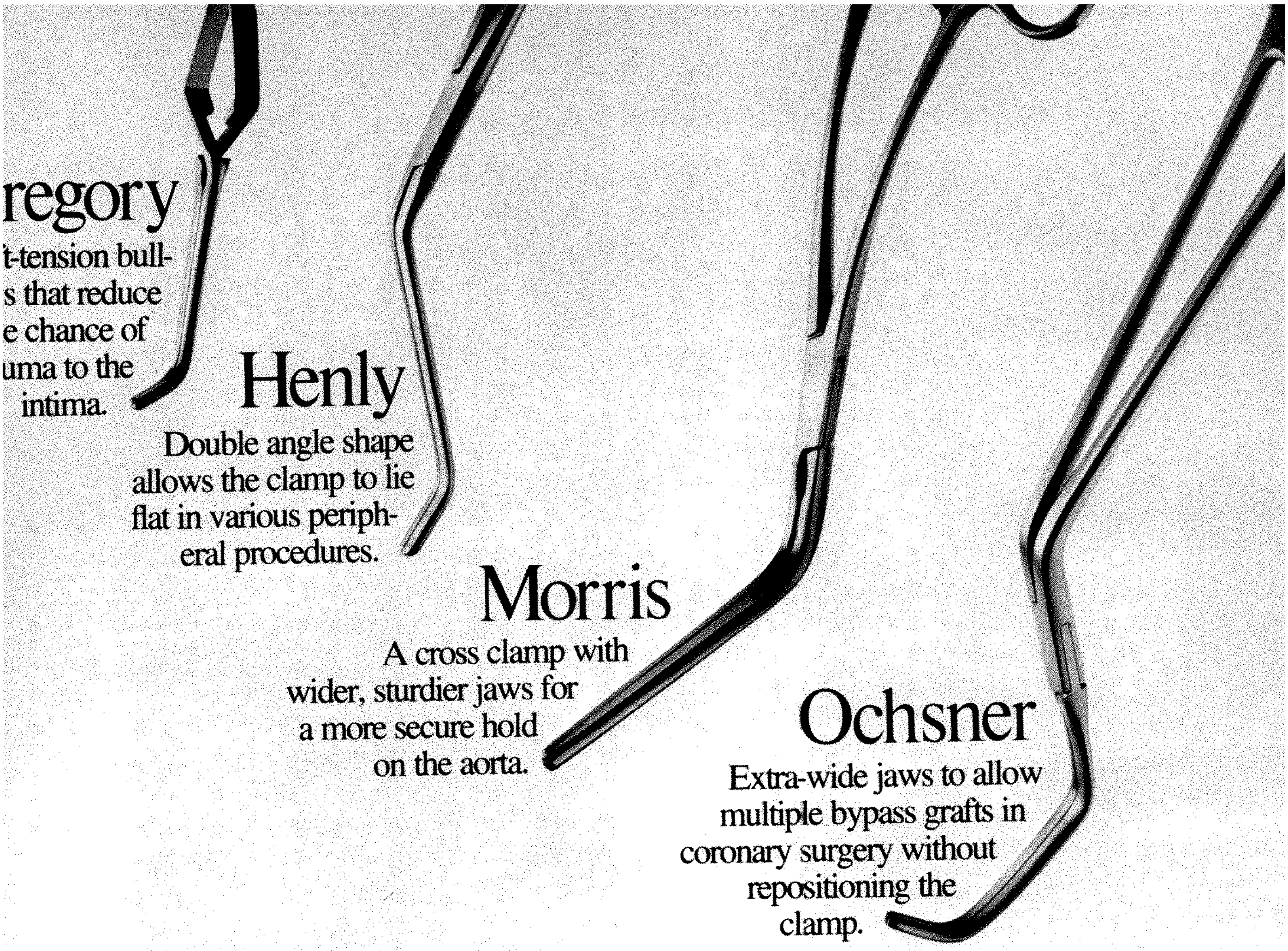

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Official Journal of The Society of Thoracic Surgeons
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Volume 30 Number 4 October 1980

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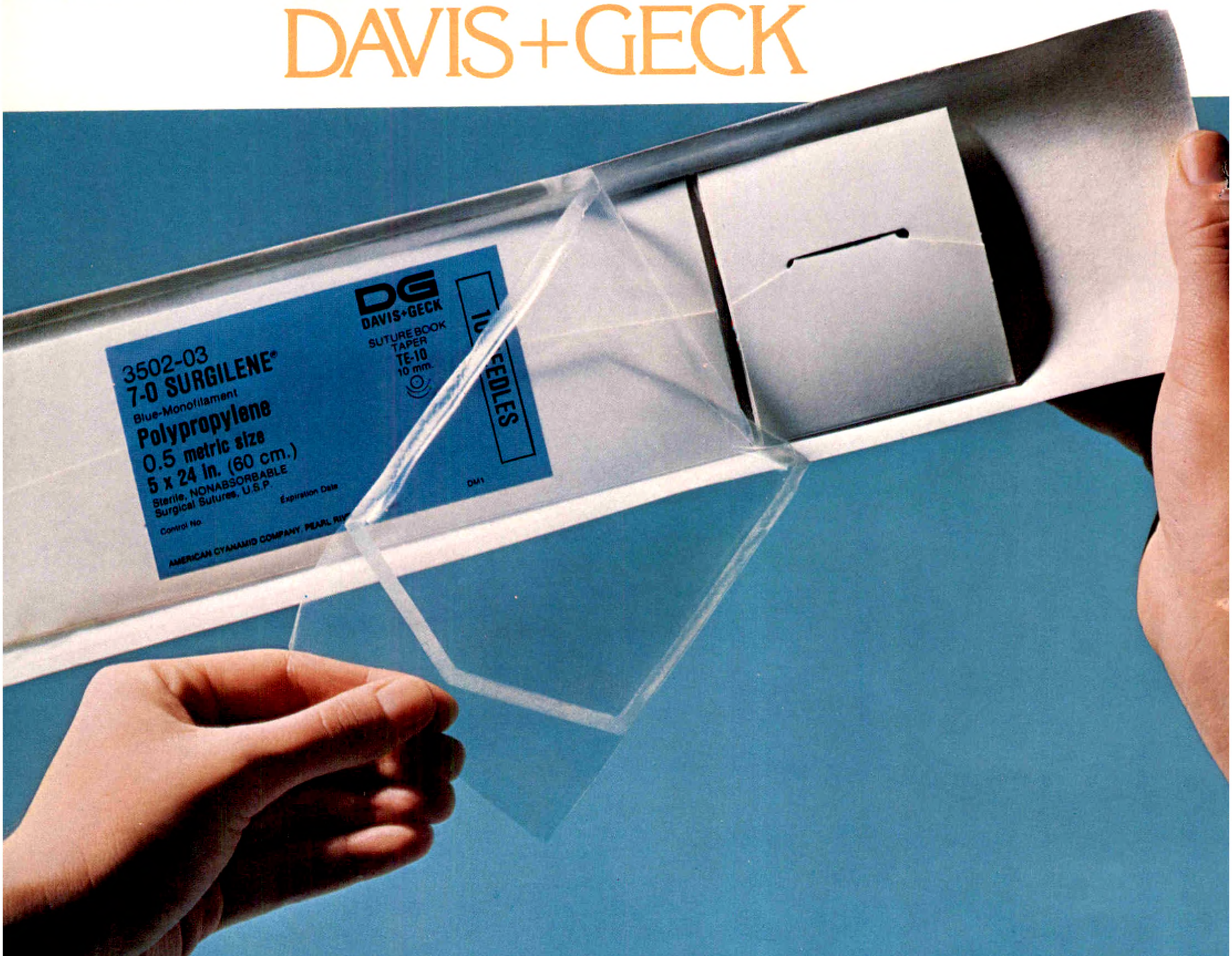

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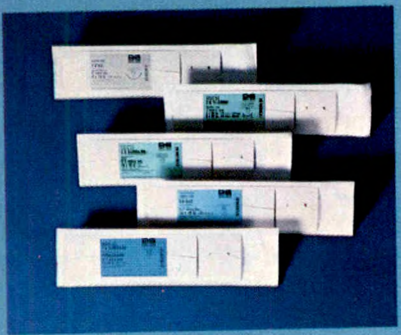

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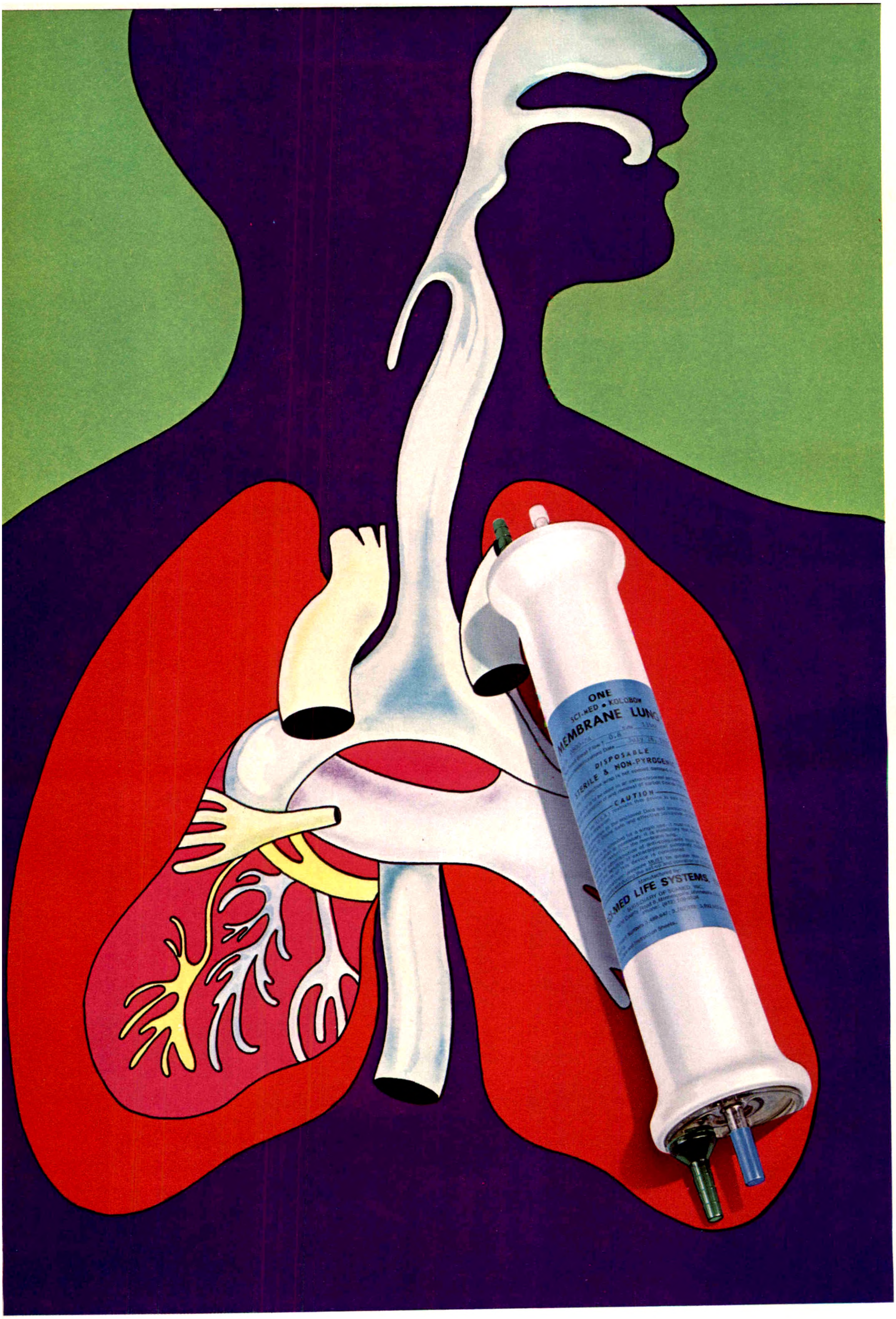
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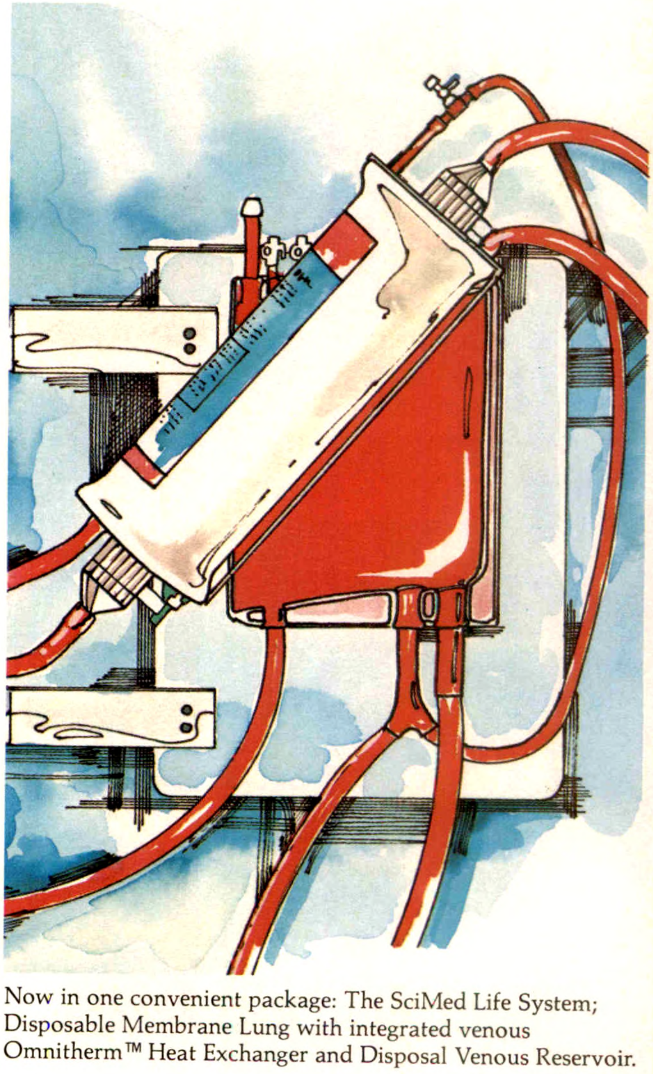

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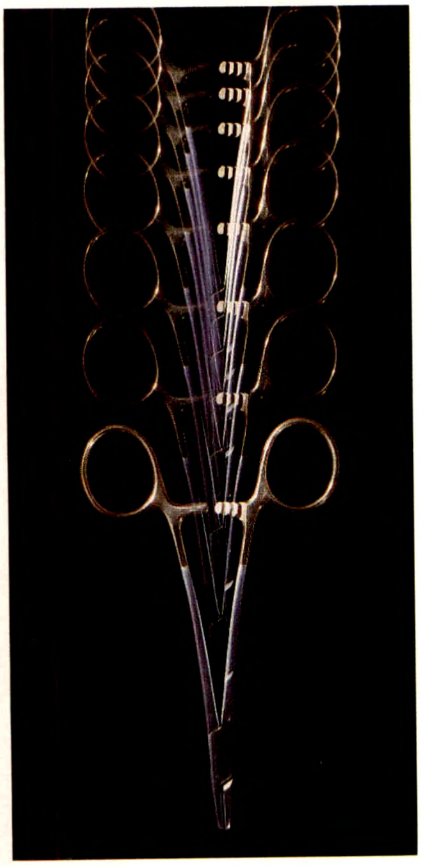

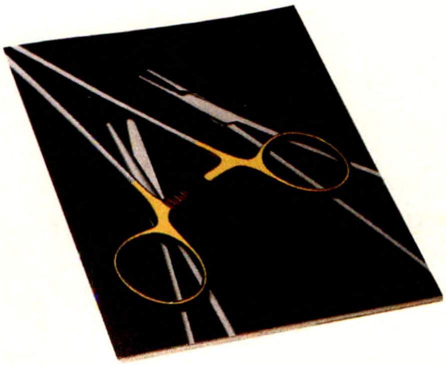

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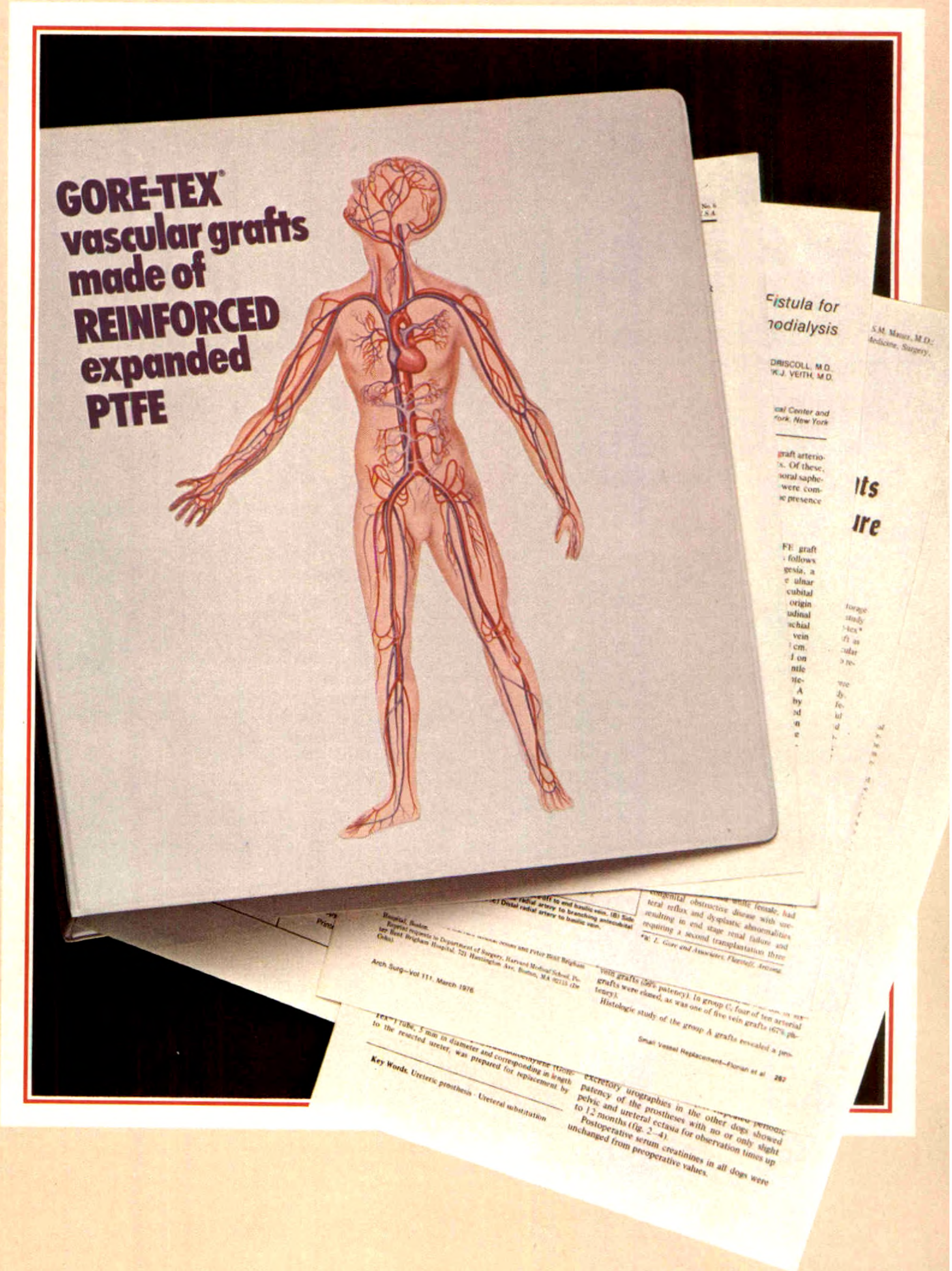
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f. **Arterial Prosthesis of Microporous Expanded Polytetrafluoroethylene for Construction of Aorta-pulmonary Shunts** Alan B. Gazzaniga, M. D., *The Journal of Thoracic and Cardiovascular Surgery 72:* 356-363, 1976; copyrighted by The C. V. Mosby Company, St. Louis, Missouri.

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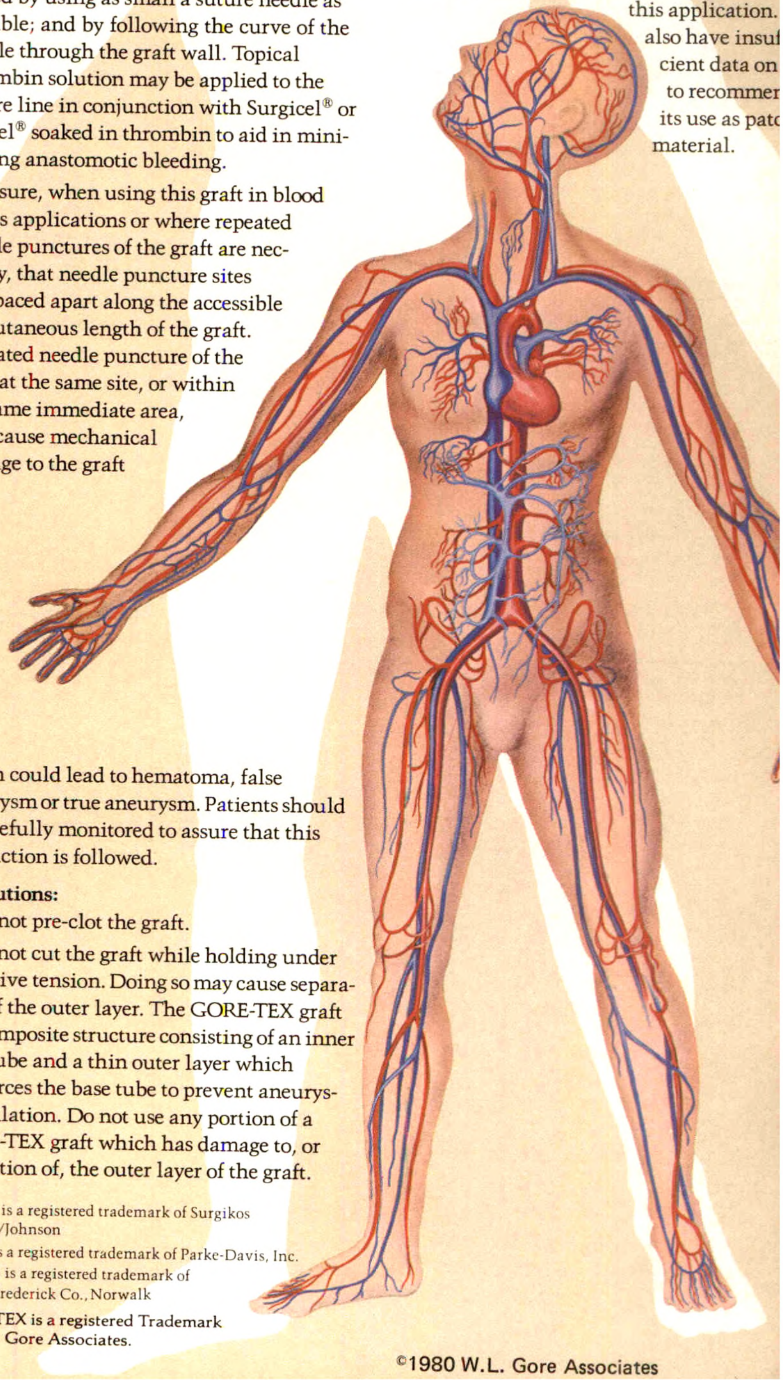

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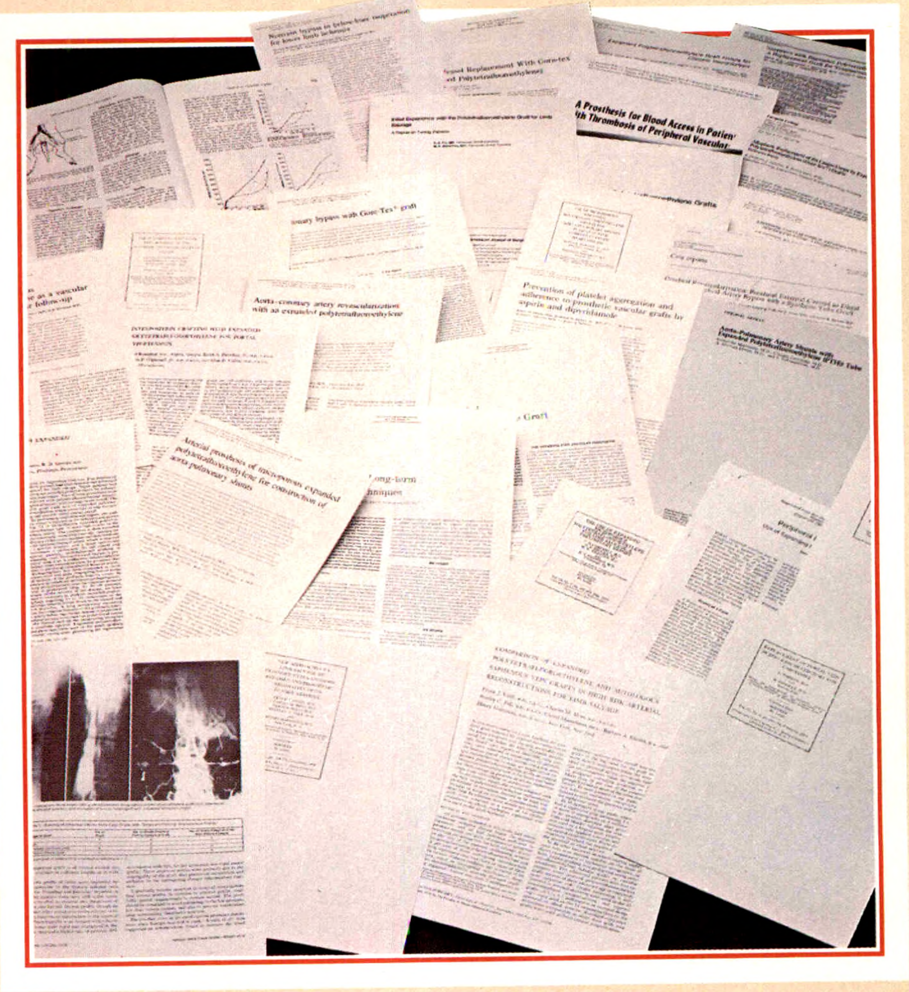

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3. A-V Fistulae
a. ☐ b. ☐ c. ☐ d. ☐
e. ☐ f. ☐ g. ☐

4. Aorta-Coronary/Pulmonary
a. ☐ b. ☐ c. ☐ d. ☐
e. ☐ f. ☐

5. Venous
a. ☐ b. ☐ c. ☐ d. ☐
e. ☐ f. ☐

6. Cerebral
a. ☐

7. Experimental
a. ☐ b. ☐ c. ☐ d. ☐

8. Miscellaneous
a. ☐ b. ☐

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EDITORIAL

The Stapling Device

Charles L. Roper, M.D.

The paper by Dorsey and associates (this issue, p 308) brings to our attention the technique for the use of the End-to-End Anastomosis (EEA) stapling device in esophagogastrectomies. The hallowed ground of traditional suture technique has been desecrated again. For the most resolute, this stapling device will always represent just another gimmick in the surgical armamentarium; others, visualizing a quick and easy way to perform an anastomosis that heretofore has required meticulous attention to detail, will accept this instrument.

Although the surgical literature is replete with reports concerning gastrointestinal anastomoses performed with the thoracoabdominal (TA) and gastrointestinal anastomosing (GIA) stapling devices, only recently have publications appeared concerning the use of the EEA stapler for esophagogastrostomy.* For those who fail to remember that any gastrointestinal anastomosis is an unforgiving one, I have a word of caution: stapled anastomoses require the same meticulous attention to detail that is required in all suture techniques.

Our techniques for the use of the EEA device vary somewhat from that employed by Dr. Dorsey's group but those differences are probably not very important and do not warrant further discussion. We have used the TA and the GIA staplers in more than 3,000 thoracic surgical procedures, but our use of the EEA device has been confined to 27 out of 30 patients undergoing esophagogastrectomy during 1978 and 1979. These procedures include both low esophagogastrostomy and supraaortic or cervical esophagogastrostomy. In the latter operations, the EEA device has proved most helpful. There have been no anastomotic leaks, a factor that may represent the most important criteria upon which to base a critical evaluation of the stapler.

We concur with Dorsey and his colleagues that the EEA device represents an important advance in esophageal operations. The time-saving factor attributed to use of the stapler is of secondary importance. Any method that will reduce suture line dehiscence, still the most frequent cause of morbidity in esophagogastrectomy, deserves our attention.

From the Division of Cardiothoracic Surgery, Washington University School of Medicine, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110.

*TA, GIA, and EEA Surgical Stapling Instruments, Auto Suture Company, Division of the United States Surgical Corporation, Norwalk, CT.

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Esophagogastrectomy Using the Auto Suture EEA Surgical Stapling Instrument

J. S. Dorsey, M.D., S. Esses, M.D., M. Goldberg, M.D., and R. Stone, M.D.

ABSTRACT **A stapling instrument, which creates end-to-end inverting anastomoses, is described for esophagogastrostomy. The inverted anastomosis is held together by a double staggered row of stainless-steel wire staples. Experience with 7 consecutive patients who underwent esophagogastrectomy for carcinoma of the distal esophagus or proximal stomach using this device is reported. Postoperative complications included atelectasis in 1 patient, cardiac failure in 1, and pneumonia in 1. A fibrotic stricture developed at the anastomotic site 5 months postoperatively in 1 patient. There were no anastomotic leaks. The stapled anastomosis takes 2 to 3 minutes to perform and seems to be at least comparable to handsewn anastomoses.**

The performance of gastrointestinal anastomoses with mechanical stapling devices has achieved popularity in the last decade. Many of these mechanical stapling devices were developed by the All Union Scientific Research Institute of Experimental Surgical Apparatuses and Instruments in Moscow. In 1970, Androsov [1] reported a mechanical stapler suitable for performing anastomoses between the esophagus and small bowel, and between the esophagus and stomach or colon or rectum. A modification of this device is the End-to-End Anastomosis* (EEA) stapler. We have successfully used the EEA stapler in 7 consecutive patients who underwent esophagogastrectomy for carcinoma of the distal esophagus or proximal stomach. In 1 patient, attempts to use the instrument were unsuccessful because of technical difficulties. We describe our technique with this instrument in esophagogastrectomies and discuss its limitations.

Material and Method

Esophagogastrectomies using the EEA stapler were performed on 7 consecutive patients at the Mount Sinai Hospital between March, 1978, and January, 1979. There were 4 men and 3 women ranging from 55 to 70 years old. Pathologically, 5 patients had adenocarcinoma and 2 had squamous cell carcinoma of the distal esophagus. Positive celiac nodes were present in 2. All of the patients were considered operable after exploration. Six patients underwent esophagogastrectomy with esophagogastrostomy, and 1 patient underwent total gastrectomy and distal esophagectomy with esophagojejunostomy.

Operative Technique

Diagnosis is made in all instances by esophagoscopy and biopsy. A left thoracoabdominal incision with transection of the costal margin is performed through the eighth interspace The diaphram is incised circumferentially 1 cm from the costal margin. The lesion is assessed for resectability and then the appropriate length of esophagus both above and below the tumor is mobilized.

In extended resections for proximal gastric lesions, a major portion of the greater omentum is dissected from the transverse colon with preservation of the right gastroepiploic arcade. Splenectomy is a useful addition to facilitate gastric mobilization. Lymphatic tissue along the superior border of the pancreas, the celiac axis, and the lesser omentum is excised en bloc. The left gastric artery is doubly ligated and divided. The point of gastric transection is selected, and the stomach is transected using the Auto Suture gastrointestinal anastomosing (GIA) stapler (Fig 1). Alternatively, a Kocher clamp is placed on the specimen side and the

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We are grateful to Mrs. Dell Walker for typing the manuscript.

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*Auto Suture Company, Division of United States Surgical Corporation, Stamford, CT.

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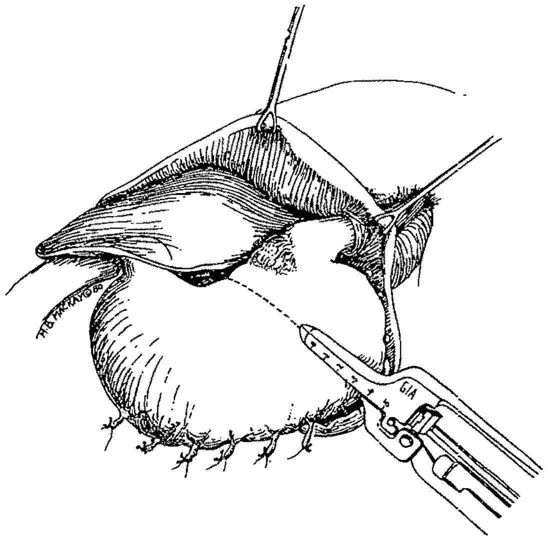

Fig 1. The stomach is transected using the Auto Suture gastrointestinal anastomosing (GIA) stapler.

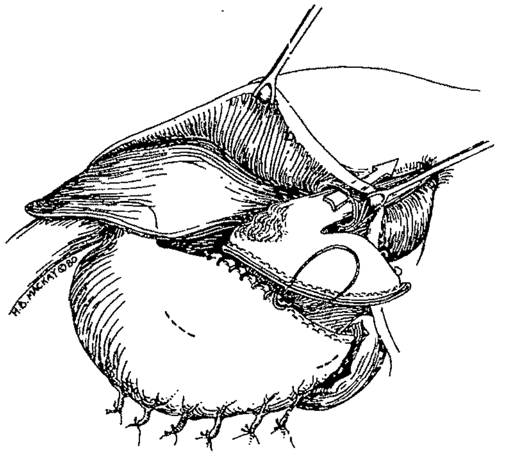

Fig 2. The resection line of the gastric remnant is oversewn with a continuous layer of locking 2-0 chromic suture and a second layer of interrupted 3-0 silk suture.

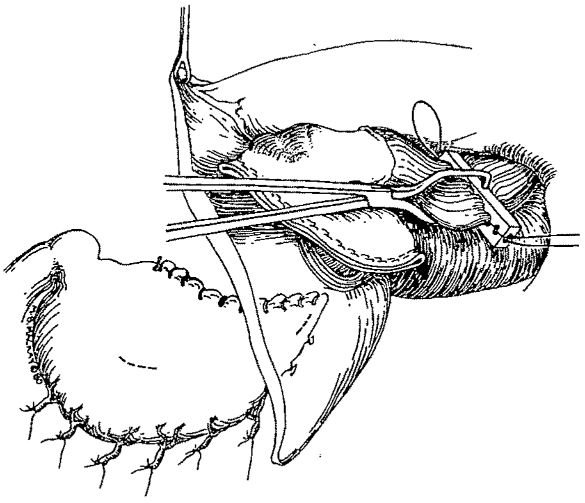

Fig 3. The esophagus is divided at least 4 cm above the lesion just below the United States Surgical's pursestring instrument. A pursestring suture is fashioned using this instrument and a 1-0 monofilament nylon suture on a Keith needle. When the needle is passed through in one direction and brought back in the other, it grasps only one wall of the esophagus on each side.

cut edge of the resection line is oversewn with a continuous layer of locking 2-0 chromic suture and a second layer of interrupted 3-0 silk suture (Fig 2).

The esophogus is divided at least 4 cm above the lesion between a Kocher clamp below and a United States Surgical's pursestring instrument above (Fig 3). A 1-0 monofilament nylon suture on a Keith needle is used to fashion a pursestring suture around the proximal end of the esophagus.

A longitudinal gastrotomy 2 to 3 cm in length is made on the antrum, and the loaded EEA stapler is inserted into the gastric remnant. A smaller stab wound about the diameter of the rod of the stapling instrument is made anteriorly at least 3 cm from the suture line of the gastric remnant and 3 to 4 cm from the greater curvature. With the rod placed fully through the stab wound and the stapler cartridge placed snugly up against the inner wall of the gastric remnant, the stapling anvil is secured on the stapler rod. The stapler rod and anvil are then inserted into the proximal esophagus (Fig 4). This is done meticulously since the esophageal end can tear if there is a major discrepancy between the diameters of the esophagus and the anvil. With the anvil inside the esophagus, the pursestring suture is tied firmly down onto the stapler rod. The stapler is adjusted so that the esophagus and gastric components of the anastomosis fit snugly between the cartridge and the anvil (Fig 5). The stapler is fired and then is readjusted to separate the cartridge and anvil slightly. The entire unit is carefully removed through the gastrotomy. The anastomosis takes 2 to 3 minutes to perform. If necessary, it can be reinforced with interrupted 3-0 silk sutures. This was necessary in only 1 patient in whom the integrity of the stapled anastomosis was questioned because of technical difficulties during its formation.

The cartridge and anvil are examined for the circular or "doughnut"-shaped tissue frag-

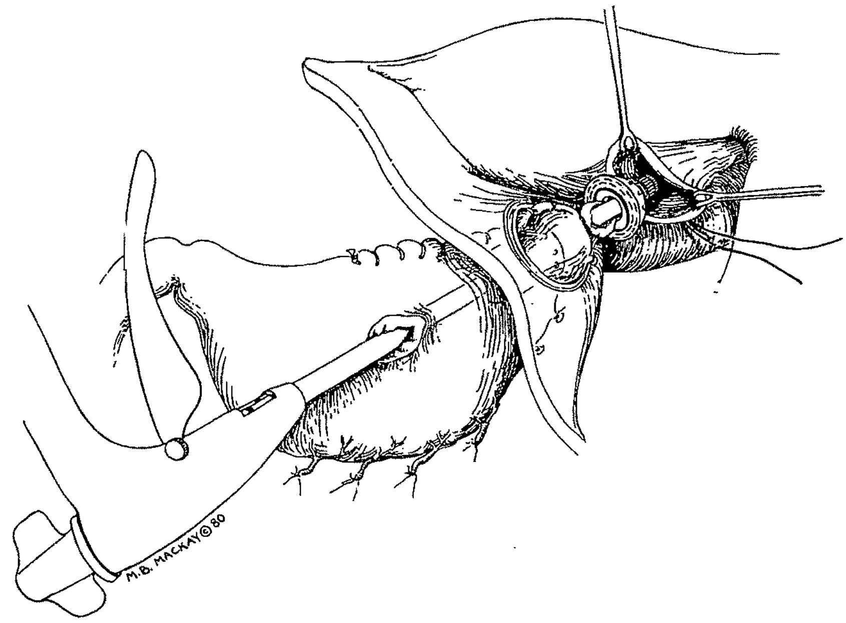

Fig 4. The EEA stapler has been advanced through the gastrotomy in the gastric remnant and the stapling anvil applied. The stapler rod and anvil are inserted into the proximal esophagus.

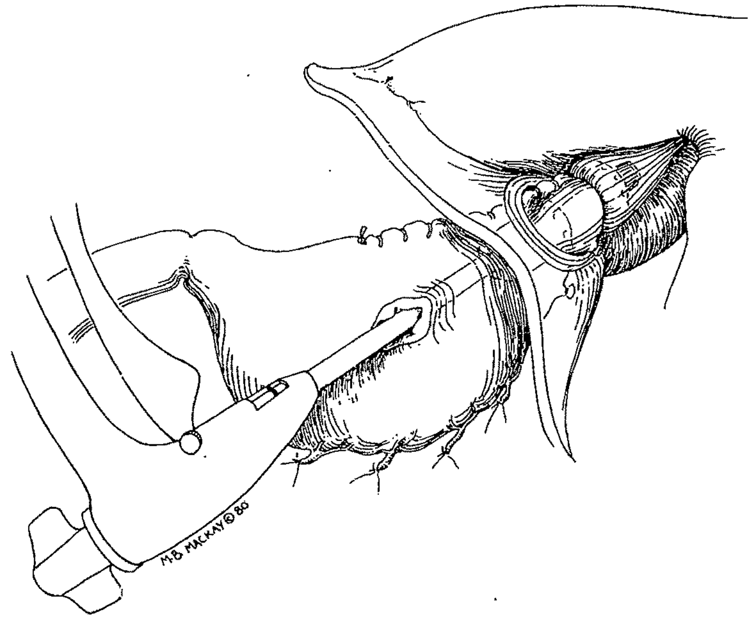

Fig 5. After the stapler is adjusted so that the esophagus and gastric components of the anastomosis fit snugly between the cartridge and anvil, the stapler is fired.

ments created by the stapler blade (Fig 6). Two circumferential tissue fragments indicate a well-fashioned anastomosis. A nasogastric tube is placed through the anastomosis, and the gastrotomy is closed. A chest tube is inserted to drain the pleural cavity. A pyloromyotomy or pyloroplasty is not performed routinely.

The anastomosis usually lies tension free above the diaphragm. Interrupted silk sutures can be used to anchor the gastric remnant to the hiatus. The diaphragm is reapproximated using interrupted 1-0 silk sutures, and the remainder of the incision is closed in layers.

Mechanical ventilatory support is used for 1 to 2 days postoperatively depending on the patient's respiratory function. Nasogastric suction is maintained for 4 to 5 days until normal bowel sounds and flatus occur. A contrast-medium

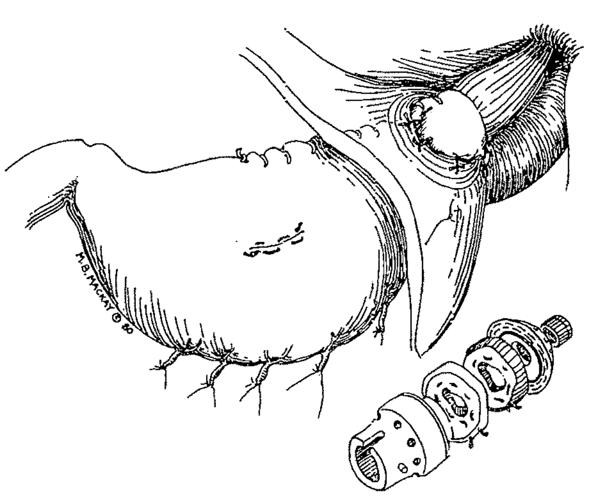

Fig 6. The stapler is carefully removed, and the cartridge and anvil are examined for circular tissue fragments or "doughnuts."

(Hypaque) swallow is then done, and if there is no evidence of anastomotic leak, the patient is started on clear fluids and advanced to a soft diet over the next few days. Antibiotics are given 1 hour preoperatively, intraoperatively, and at 6-hour intervals postoperatively for 24 hours.

Results

There were no immediate postoperative deaths in this series. One patient died of metastatic disease 6 months postoperatively. One patient had a mild febrile course which was thought to be related to atelectasis. This cleared with respiratory physiotherapy. One patient had difficulty with cardiac failure; it was managed successfully with digoxin and diuretics. One patient had a prolonged hospitalization because of a wound infection and pneumonia of the left lower lobe. Five months after this patient was discharged, a fibrotic stricture developed at the anastomotic site and was treated successfully by a single bougienage.

Comment

Von Petz [11], in 1927, published his results with a new clamp, which provided protection from spillage during gastrointestinal resection. A modification of this instrument is still in use in many hospitals. These early instruments were bulky and sometimes difficult to use.

In the Soviet Union in the 1950s, the All Union Scientific Research Institute of Experimental Surgical Apparatuses and Instruments developed several mechanical stapling devices for use in gastrointestinal and thoracic operations. The use of these instruments has been described by Ravitch and colleagues [7, 8] and Steichen [10]. The GIA and thoracoabdominal (TA) staplers allow sealed transections of stomach or bowel. By various maneuvers, these instruments can be used to produce side-to-side and functional end-to-side anastomoses.

The EEA instrument was designed for end-to-end anastomoses, and its use in various gastrointestinal anastomoses has been described [6, 9]. We have presented our technique of using the EEA stapler in esophagogastrectomies. Although there have been problems with its use in colorectal anastomoses [3], it appears to be very helpful in esophagogastrostomy. The instrument is slightly awkward to use because of its size, but facility seems to improve with experience. We have used the 31.5 mm diameter cartridge and anvil. This produced technical problems in the esophagus with a small diameter. Two smaller cartridge and anvil diameters are now commercially available, and this should alleviate the problem of size discrepancy between the esophageal lumen and the anvil.

No attempts were made to cover the anastomosis with pleura or adjacent tissue. Androsov [1] suggested covering the anastomosis in the abdomen with omentum. Reinforcing the anastomosis with interrupted sutures has been considered, but we have not found this necessary on a routine basis. In one instance, a corner of the anastomosis was reinforced with silk sutures because examination of the tissue remnants in the anvil and cartridge revealed a tissue gap suggestive of incomplete fashioning of the anastomosis.

Anastomotic complications in esophagogastrectomy were reviewed by Chassin [2] in 1978. Pooling the data from thirteen reports in the literature, he found the average mortality following esophagogastrectomy to be 20%, with approximately 10% of these related to leaks from the esophagogastric anastomosis. Fewer anastomotic complications are reported with an end-to-side esophagogastrostomy (less than 2% fatal leak rate) than an end-to-end esophagogastrostomy. In some cases, Chassin used mechanical stapling devices to fashion his

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anastomoses. No comparison between the handsewn and stapled anastomoses was reported. In the stapled cases, the Auto Suture GIA stapling device was used to fashion the posterior portion of the esophagogastric anastomosis. The remaining anterior defect was closed by triangulation with two applications of the Auto Suture TA-55 stapling device. As we have described, fashioning the end-to-side anastomosis with the Auto Suture EEA stapler requires only one application of an instrument. This instrument performs esophagogastrostomy easily and quickly. Latimer and associates [5] and Gutsman [4] analyzed the clinical results of using stapling techniques in more than 4,000 operations. The former reported a stapler-related complication rate of 1.9% and a 1% mortality in 256 stapling procedures in 104 surgical patients who underwent gastrointestinal operation. Gutsman compared 10,358 handsewn gastric resections for carcinoma of the stomach with 668 gastric resections using mechanical staplers. The reported mortality was 10.4% in the former and 3.6% in the latter. A similar comparison in resections for peptic ulcer disease (42,528 patients in the handsewn resections and 958 patients in the stapled resections) showed a mortality of 3.2% in the former and 1.0% in the latter.

Our series is presently too small to warrant comparison with hand-sewn resection. Our present experience, however, does suggest the applicability of the Auto Suture EEA stapler in esophagogastrectomy. Further clinical use should allow comparisons between the handsewn and stapled anastomosis.

Addendum

Our experience with the EEA stapler has been extended to include a total of 15 consecutive patients. Nine patients underwent esophagogastrectomy with esophagogastrostomy; 5 patients underwent total gastrectomy and distal esophagectomy (with loop esophagojejunostomy in 2 and roux-en Y esophagojejunostomy in 3); and 1 patient had a non-reversed Beck gastric tube esophagogastrostomy bypass for unresectable carcinoma. No anastomotic leaks or postoperative deaths have occurred in our series.

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Discussion

DR. JAMES R. JUDE (Miami, FL): I compliment the authors on this discussion of a valuable tool. I have used it in 6 patients but have found it takes a little longer than 2 or 3 minutes to make the anastomosis. To pull a little lever and discharge the staples may require only a few seconds, but to actually get the pursestring sutures in properly and to make sure there is a proper cuff of tissue takes a little longer. However after the first two or three applications, the technique becomes easier. This instrument was developed, as you may know, for low anterior bowel resections. If it should prove to not work well with thoracic procedures, it can always be used with abdominal ones.

The stapler has worked very well for surgeons doing colorectal operations, and it really simplifies what sometimes can be a very difficult surgical anastomosis in the chest. I have done esophagogastrectomy through a right thoracotomy and a midline abdominal incision. A very high anastomosis can be obtained up under the aortic arch. The Auto Suture EEA stapler is a very valuable tool, and I compliment the authors again.

DR. DORSEY: Difficulty with the pursestring suture certainly has not been a major problem in our series. I add that we have not routinely used a drainage procedure with our esophagogastrectomies.

Interruption of Multiple Accessory Conduction Pathways in the Wolff-Parkinson-White Syndrome

Takashi Iwa, M.D., Tatsuo Magara, M.D., Yoh Watanabe, M.D.,
Michio Kawasuji, M.D., and Takuro Misaki, M.D.

ABSTRACT **Of 35 patients with Wolff-Parkinson-White syndrome operated on, 5 were seen with two accessory conduction pathways each; all of these were successfully interrupted. In one patient, one accessory conduction pathway each was located in the right and left side of the heart; in the other 4, both pathways were confined to the right side. In 2 patients with unilateral (right side) multiple accessory conduction pathways, Ebstein's anomaly was also present.**

In 1 patient with Ebstein's anomaly, the second unilateral accessory conduction pathway was discovered intraoperatively and was successfully interrupted. The remaining 4 patients required a second operation to interrupt the other pathway. A delta wave completely different from the preoperative one appeared 4 to 10 days after interruption of the first major pathway, and the second operation was performed 14 days, 42 days, four months, or five years after the first operation. All 5 patients survived, and long-term follow-up revealed no signs of morbidity.

Until approximately ten years ago, symptomatic drug therapy constituted the only method of treating tachycardia in patients with Wolff-Parkinson-White (WPW) syndrome [33]. In 1969, Sealy and co-workers [29] and in the following year, my associates and I [15] reported the successful radical repair of the syndrome by surgically interrupting the accessory conduction pathway. While surgical therapy was initially confined to right cardiac type WPW, later it was extended to include the left cardiac [19] and septal types and even the infant WPW syndrome [17]. Various electrophysiological examinations [5, 6, 8, 13] and improvements in surgical techniques [11, 12, 31] have made radical repair possible in patients with WPW syndrome.

However, problems remain in patients with multiple accessory conduction pathways. By August, 1979, we had performed surgical repair of the WPW syndrome in 35 patients. Among these, there were 5 with multiple accessory conduction pathways, which presented challenging problems. Here we are reporting the cases of these 5 patients, with special reference to the most useful studies for the detection and treatment of multiple accessory conduction pathways in the WPW syndrome.

Material and Methods

Between 1969 and 1979, we surgically treated 35 patients with WPW syndrome. There were 5 with multiple accessory conduction pathways (Table 1), and in 2 of these 5, Ebstein's anomaly was present. One patient was a resident of our city; the other 4 were referred by cardiologists from other areas in Japan. All patients were male; they ranged from 15 to 36 years old. All had experienced frequent and severe tachycardia despite extensive medication.

Routine electrophysiological studies were performed as previously detailed by us [10, 13, 16, 18, 23] and others [6, 8] (Table 2). These studies included electrocardiography, vectorcardiography, echocardiography, body surface mapping, preoperative intracavitary mapping with or without cardiac stimulation, and intraoperative epicardial and endocardial mapping.

Case Reports

Patient 1

A 36-year-old man had a past history of epileptic seizures. He had experienced tachypnea and palpitation episodes since he was 19 years old. At age 36 years, reciprocating tachycardia and atrial fibrillation were noted, and a diagnosis of

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Table 1. Data on 5 Patients with Multiple Accessory Conduction Pathways

Patient No., Age (yr), Sex	Combined Disease	Localization of Pathways[a]	Reappearance of Delta Wave (d after first op)	Interval between Two Operations	Results
1. 36, M	Epilepsy	R posterior free wall R anterior free wall	10	4 mo	Complete repair
2. 29, M	...	R anterior free wall R anterior septal wall	4	42 d	Complete repair
3. 18, M	...	L posterior free wall R anterior septal wall	5	14 d	Complete repair
4. 15, M	Ebstein's anomaly	R posterior septal wall R anterior septal wall	Immediate[b]	...	Complete repair
5. 26, M	Ebstein's anomaly	R posterior free wall R posterior septal wall	10	5 yr	Complete repair

[a] Upper line indicates the first major accessory conduction pathway; lower line indicates the second minor pathway.
[b] No delta wave, but tachycardia with tight QRS interval appeared.

Table 2. Data from the Electrophysiological Study

Patient No.	Refractory Period of ACP (msec)	Shortest R-R during AF (msec)	Shortest Stimulation —Delta Wave (msec)	Retrograde Conduction during RV Pacing (msec)
1	325	196	HRA, 100	Lat RA 160
2	300	240	HRA, 110	NP
3	250	200	CS, 75	NP
4	...	240	...	...
5	...	...	...	...

ACP = accessory conduction pathway; AF = atrial fibrillation; RV = right ventricle; HRA = high right atrium; Lat RA = lateral right atrium; NP = not particular; CS = coronary sinus.

WPW syndrome was made. An electrocardiogram (ECG) revealed the shortest R-R interval during atrial fibrillation to be 196 msec. The patient was referred to us for surgical repair.

As shown in Figure 1, a preoperative ECG revealed the initial force of the delta wave to be isoelectric (±) in leads V_1 and III, a negative wave in aVF, and a positive wave in lead II. Therefore, we suspected the accessory conduction pathway was localized in the right posterior wall [14]. Epicardial mapping (Fig 2) in sinus rhythm and during atrial pacing confirmed the early excitation area to be located at the suspected site.

A 4 cm incision along the tricuspid annulus in the area corresponding to that of the early excitation resulted in normalization of the ECG. After the interruption, tachycardia was not elicited by atrial or ventricular pacing on the operating table. However, on the tenth postoperative day, a delta wave during sinus rhythm (see Fig 1) and reciprocating tachycardia appeared. The initial force of the delta wave was similar to that noted on the preoperative ECG, but the polarity of the wave was changed from negative deflection to isoelectric in lead III (see Fig 1). Therefore, the existence of an accessory conduction pathway at the right ventricular free wall was suspected.

Epicardial mapping (see Fig 2) during the second operation four months later, revealed the early excitation area to be located at the right ventricular free wall. This finding was completely different from that obtained at the first operation and was consistent with the results of endocardial mapping during right ventricular pacing. An incision of approximately 3 cm was made in this part of the tricuspid annulus and resulted in an ECG with a normal pattern and in the disappearance of the

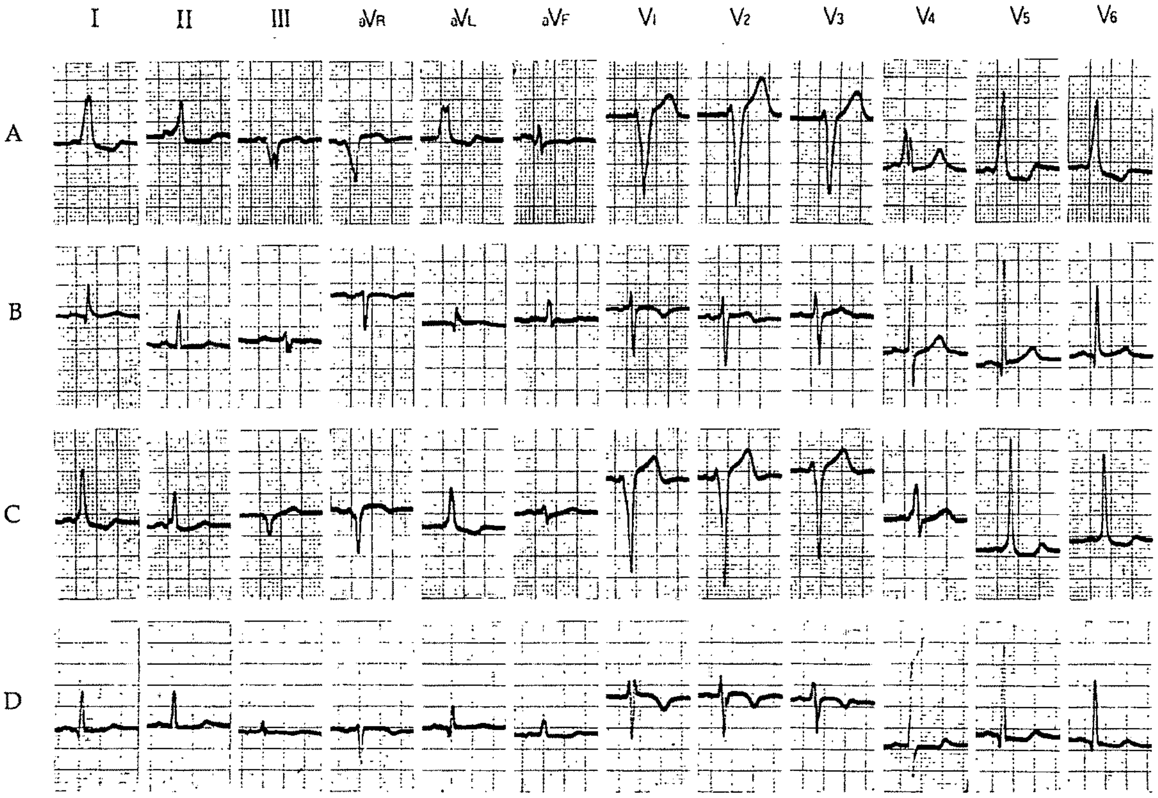

Fig 1. (Patient 1.) Electrocardiogram made (A) before the first operation, (B) 1 day postoperatively, (C) 10 days postoperatively, and (D) after the second operation. For details, see text.

delta wave and the tachycardia. No postoperative recurrence has been noted.

Patient 2

A 29-year-old man experienced his first tachycardia attack when he was 8 years old. The attacks had occurred almost daily since he was 27 years old, despite medical treatment.

On preoperative ECG, the initial force of the delta wave was positive in leads I, II, III, and aVF, and isoelectric in leads V_1 and V_2. This led us to suspect that an accessory conduction pathway was located at the right ventricular free wall. Intraoperative epicardial mapping showed early excitation at the upper portions of the right free wall close to the right anterior septal wall. Further intraoperative endocardial mapping during reciprocating tachycardia showed the early excitation area to be located in the right ventricular free wall (Fig 3), and an incision of about 4 cm was made in this part of the tricuspid annulus. An ECG made immediately after operation showed a pattern of left bundle-branch block, but the delta wave had disappeared. Tachycardia was not provoked by atrial or ventricular pacing.

However, it reappeared on the fourth postoperative day. A postoperative ECG showed the initial force of the delta wave to be positive in leads I, II, III, and aVF, and negative in lead V_1. These findings were different from those of the preoperative ECG and caused us to suspect the presence of an accessory conduction pathway at the right anterior septal wall. Subsequently, reciprocating tachycardia also reappeared.

The patient underwent reoperation on the forty-second day after the first operation. Since the delta wave disappeared temporarily shortly after exposure of the heart, epicardial mapping was not done. However, reciprocating tachycardia appeared after initiation of cardiopulmonary bypass, and right atrial endocardial mapping was performed. As expected from the ECG before the second operation, the early excitation area was located at the right anterior septal wall (Fig 4), and an incision of about 3 cm

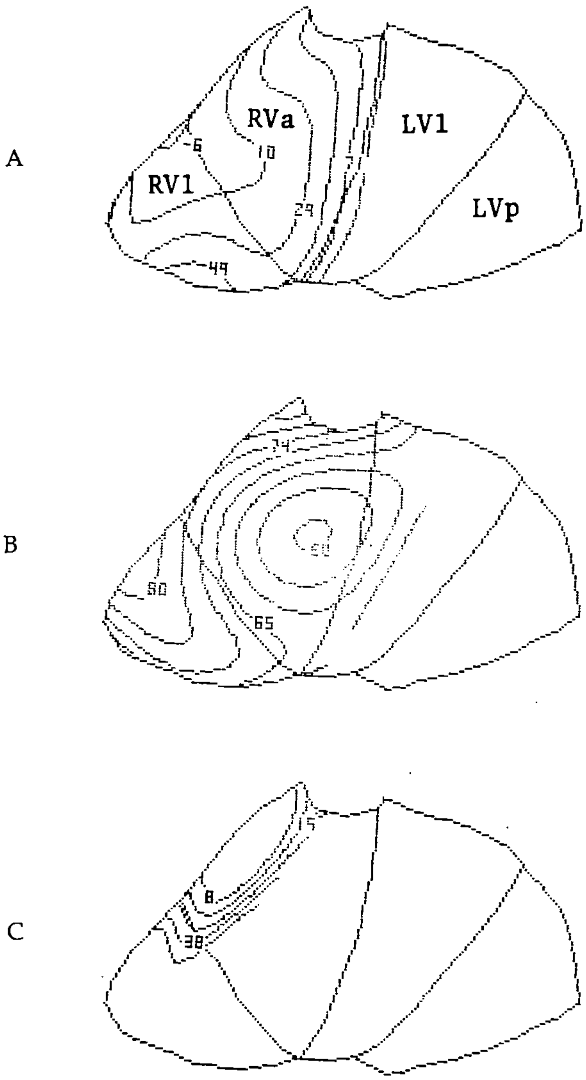

Fig 2. (Patient 1.) Epicardial mapping at several stages. (A) During the first operation. The pathway was demonstrated at the isochronous line marked −6. (B) After the accessory conduction pathway was interrupted, a normal pattern was obtained. Activation sequence of the ventricle is normal as shown as isochronous line 50, *along the groove between the right and left ventricles. (C) During the second operation. The earliest excitation was located at the right ventricular free wall, shown by isochronous line* 8. *Numbers are expressed in milliseconds before and after reference point.* (RVa = *anterior right ventricle;* RVl = *lower right ventricle;* LVl = *lateral left ventricle;* LVp = *posterior left ventricle.)*

was made along the tricuspid annulus in this part. After the second operation, reciprocating tachycardia did not recur even during atrial or ventricular pacing. While an ECG made during the long-term follow-up showed left bundle-branch block, the delta wave and the tachycardia attacks had completely disappeared. The

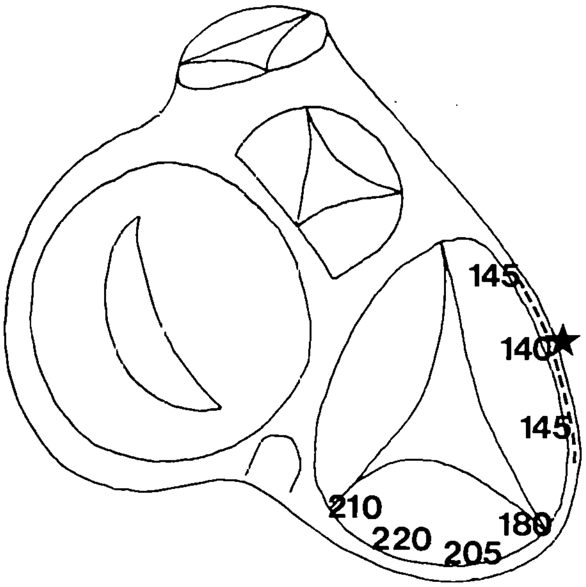

Fig 3. (Patient 2.) Retrograde activation during reciprocating tachycardia (first operation). The earliest excitation (140 msec) was located at the lateral free wall of the right ventricle. This finding corresponded well with the epicardial mapping. Figures placed around the atrioventricular ring are atrial activation sequences. (Broken line = *incision.)*

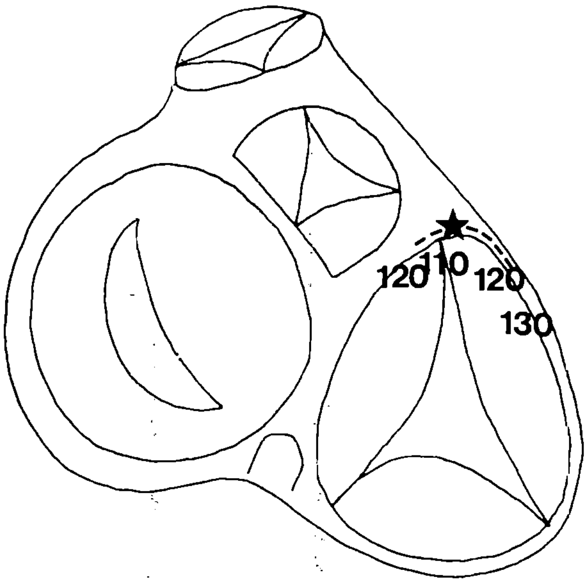

Fig 4. (Patient 2.) Retrograde activation during reciprocating tachycardia (second operation). The earliest excitation (110 msec) was located at the right anterior septal wall. This finding corresponded well to ECG findings. (Broken line = *incision.)*

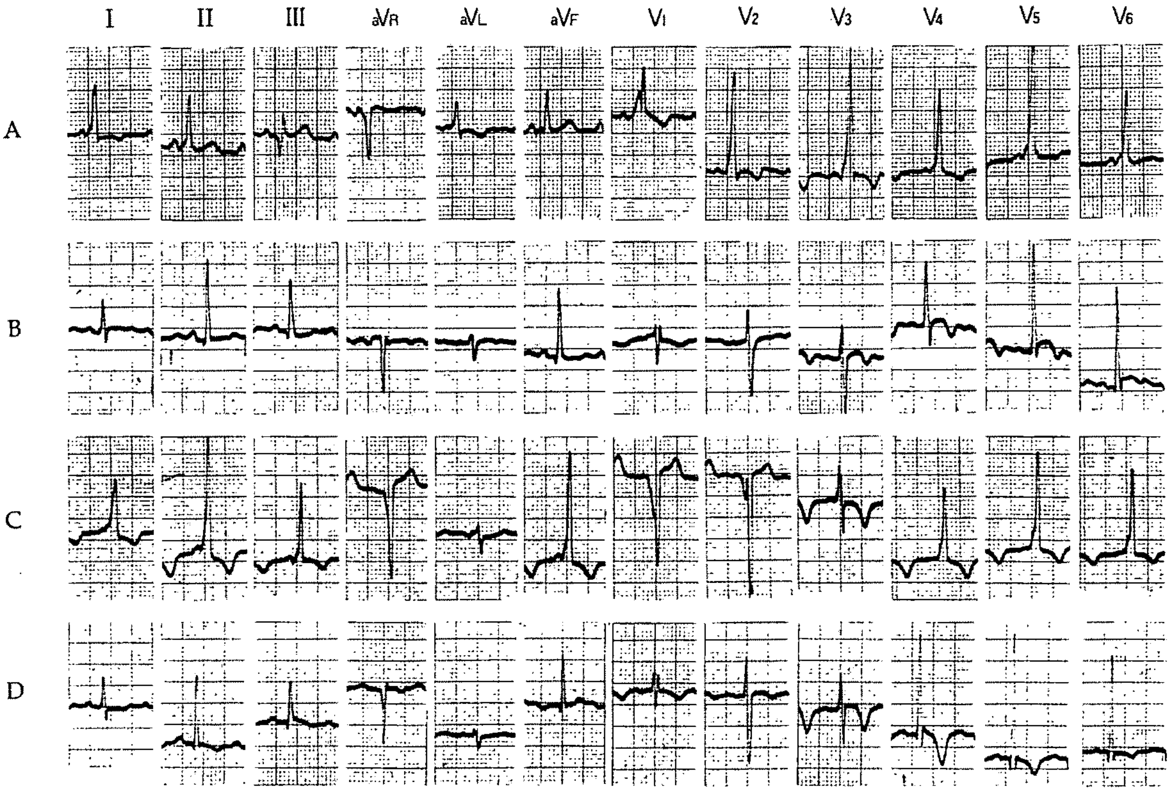

Fig 5. (Patient 3.) Electrocardiograms made (A) before the first operation, (B) 1 day after interruption of the first accessory conduction pathway, (C) 5 days after the first operation, and (D) after the second operation. For details, see text.

left bundle-branch block must have been present before the first operation since no surgical intervention took place in the left heart.

Patient 3

An 18-year-old man experienced his first tachycardia attack when he was 10 years old, and he was diagnosed as having WPW syndrome. Medical treatment was administered, but ventricular tachycardia began to occur when he was 18 years old, frequently necessitating direct current cardioversion. Later, two episodes of ventricular fibrillation took place, and emergency cardiopulmonary resuscitation led to recovery. The patient was subsequently referred to our clinic for surgical treatment.

An ECG (Fig 5) suggested an accessory conduction pathway at the left ventricular free wall, and a vectorcardiogram revealed abnormal movement of the left ventricular posterior wall characteristic of the left cardiac type WPW syndrome. Pacing study, using a coronary sinus catheter, revealed the early excitation to be located at the left posterior wall. The electrophysiological study showed the tachycardia impulse to be conducted in an anterograde fashion through the accessory conduction pathway on the left side and that it returned retrograde over the His bundle, thus forming a reentry circuit. On ECG, electric stimulation of the right atrium showed almost no change in the waveform and right ventricular pacing revealed no early excitation in the right atrial endocardium. Therefore, the presence of an accessory conduction pathway in the right side of the heart was excluded.

Intraoperative epicardial mapping during sinus rhythm (Fig 6) located the early excitation area at the left posterior wall and confirmed the results of preoperative studies. An incision of approximately 4 cm was made in the mitral annulus in the area corresponding to that of the early excitation. After the heart began beating, an ECG revealed disappearance of the delta wave, and epicardial mapping showed a normal conduction pattern (see Fig 6). Atrial or

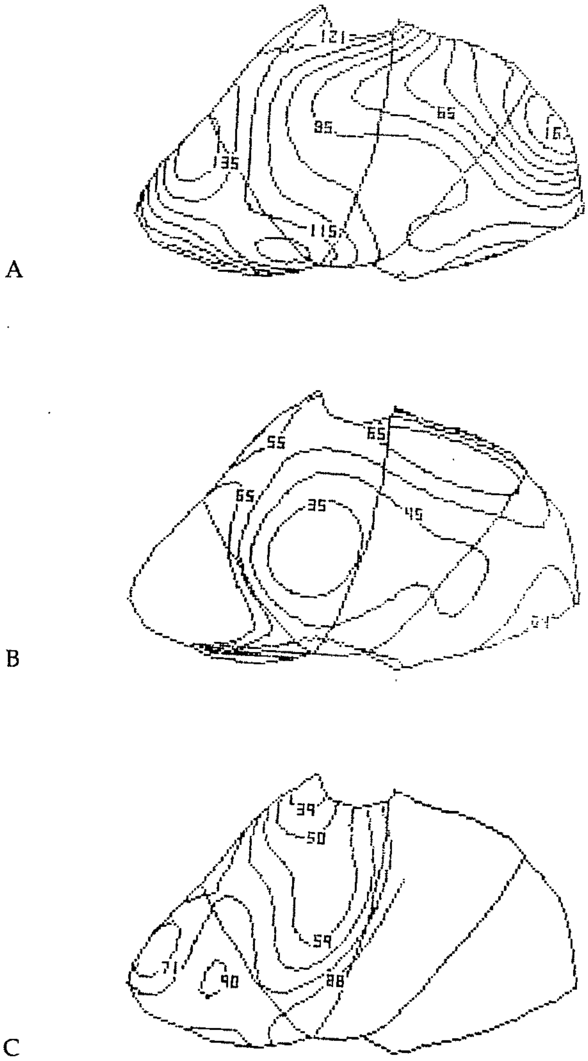

Fig 6. (Patient 3.) Epicardial mapping (A) before the interruption. (B) After the interruption, a normal pattern was obtained. (C) Before the second operation. The preexcitation was located at the right anterior septal wall.

ventricular stimulation failed to induce reciprocating tachycardia. A normal ECG was obtained for 4 days, but on the fifth postoperative day, an ECG showed a delta wave different from the preoperative one. Its initial force was positive in leads II, III and aVF, and negative in leads V_1 and V_2 (see Fig 5). These findings suggested the existence of an accessory conduction pathway on the right anterior septal wall. While reciprocating tachycardia did not occur spontaneously, it could be induced by atrial and ventricular pacing.

Reoperation was performed on the fourteenth day after the first operation. Intraoperative epicardial mapping (see Fig 6) revealed early excitation at the right anterior septal wall; an incision about 3 cm long was made along the tricuspid annulus in the area corresponding to the early excitation. Thereafter, the delta wave disappeared completely, and reciprocating tachycardia did not occur at all.

Patient 4

This patient has been reported in detail previously [16, 20]. A 15-year-old boy who also had Ebstein's anomaly had initially been treated at another hospital with digitalis, procainamide, and ajimarine to control the tachycardia. However, increased medication failed to prevent the tachycardia attacks. Right atrial overdrive stimulation or direct current cardioversion succeeded in controlling the tachycardia, but it resumed within a few minutes. Then it lasted almost all day so that complete bed rest was necessary.

An ECG showed the initial force of the delta wave to be negative in leads V_1, II, III, and aVF, leading us to suspect that the accessory conduction pathway was located at the right posterior septal wall. An ECG during tachycardia also showed the delta wave, but the QRS interval was wider. This wider QRS pattern and the electrical axis of the heart were basically the same as those obtained during sinus rhythm. Preoperative electrophysiological study was not performed because the patient complained of anxiety and discomfort due to the tachycardia.

Intraoperative epicardial mapping localized the early excitation area at the right posterior septal wall; this was consistent with preoperative ECG findings. No other area of the right ventricle showed early excitation.

With the heart beating, a small incision was made along the annulus of the tricuspid valve in the area corresponding to the early excitation. The delta wave disappeared immediately, and the cardiac axis changed. However, a tachycardia attack of 168 beats per minute set in soon, exhibiting the same ECG pattern as that obtained immediately after the interruption. Therefore, we suspected the presence of another accessory conduction pathway working retrograde, which produced a reentry circuit together with the normal conduction

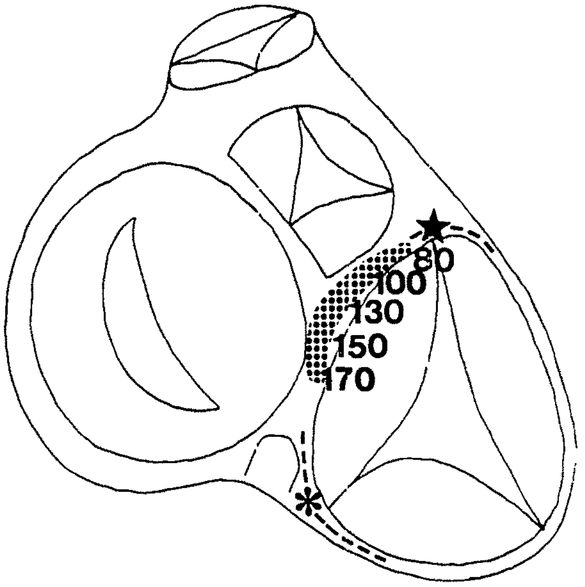

Fig 7. (Patient 4.) Retrograde activation during reciprocating tachycardia. The earliest excitation (80 msec) was located at the right anterior septal wall. (★ = site of the second accessory conduction pathway; ✱ = site of the first accessory conduction pathway; broken line = *incision.)*

system. A bipolar electrode was applied at the tricuspid annulus for endocardial mapping. An early excitation area was obtained at the right anterior septal wall, indicating the presence of another accessory conduction pathway. Reciprocating tachycardia was confirmed to occur retrograde through this pathway.

Avoiding the His bundle, we incised the tricuspid annulus in this area, and the tachycardia disappeared (Fig 7). There was no change in the ECG pattern. Since the patient also had Ebstein's anomaly, the tricuspid valve was replaced with a 35 mm Hancock xenograft and the atrialized ventricle was plicated. Postoperative ECG showed a right bundle-branch block pattern, but the delta wave had disappeared and no further tachycardia attacks occurred [16, 20].

Patient 5

A 26-year-old man with WPW syndrome and Ebstein's anomaly experienced reciprocating tachycardia often and atrial fibrillation occasionally. On preoperative ECG (Fig 8), the initial force of the delta wave showed negative deflection in leads II, III, and aVF, and was isoelectric in lead V_1, leading us to suspect the presence of an accessory conduction pathway on the right posterior wall. No detailed electrophysiological study was done because the patient was treated in 1973 before these studies had been established. After the heart was exposed by a median sternotomy, epicardial mapping was performed and the early excitation area was found to be located at the atrioventricular groove of the right ventricular base, a finding consistent with the preoperative ECG finding.

The right atrium was opened under cardiopulmonary bypass, and two bipolar electrodes, 2 mm apart, were applied at the annulus of the tricuspid valve. A sharp electrical potential originating from the accessory conduction pathway was recorded just before the appearance of the delta wave [9]. When an endocardial incision (approximately 3 cm in length) was made along the tricuspid annulus, the delta wave disappeared and the ECG axis converted to normal. Because the tricuspid valve deformity was mild, no surgical treatment was performed.

Postoperative epicardial mapping showed that although a right bundle-branch block pattern appeared in the ECG, the previous site of the early excitation area at the right diaphragmatic wall had disappeared. The accessory conduction pathway was thought to have been completely interrupted.

On the tenth postoperative day, a delta wave completely different from the preoperative one appeared. Its initial force was isoelectric in leads II, III, and aVF, and there was a positive deflection in leads aVL, V_1, and V_2. Postoperative attacks of reciprocating tachycardia did occur, but they were decreased greatly in number and severity.

The patient was reoperated on five years after the first operation. All preoperative and intraoperative studies indicated that the second accessory conduction pathway was located at the right posterior septal wall, and it was interrupted without any difficulty. The ECG changed to a normal pattern with right bundle-branch block, the delta wave had disappeared (see Fig 8), and reciprocating tachycardia did not recur.

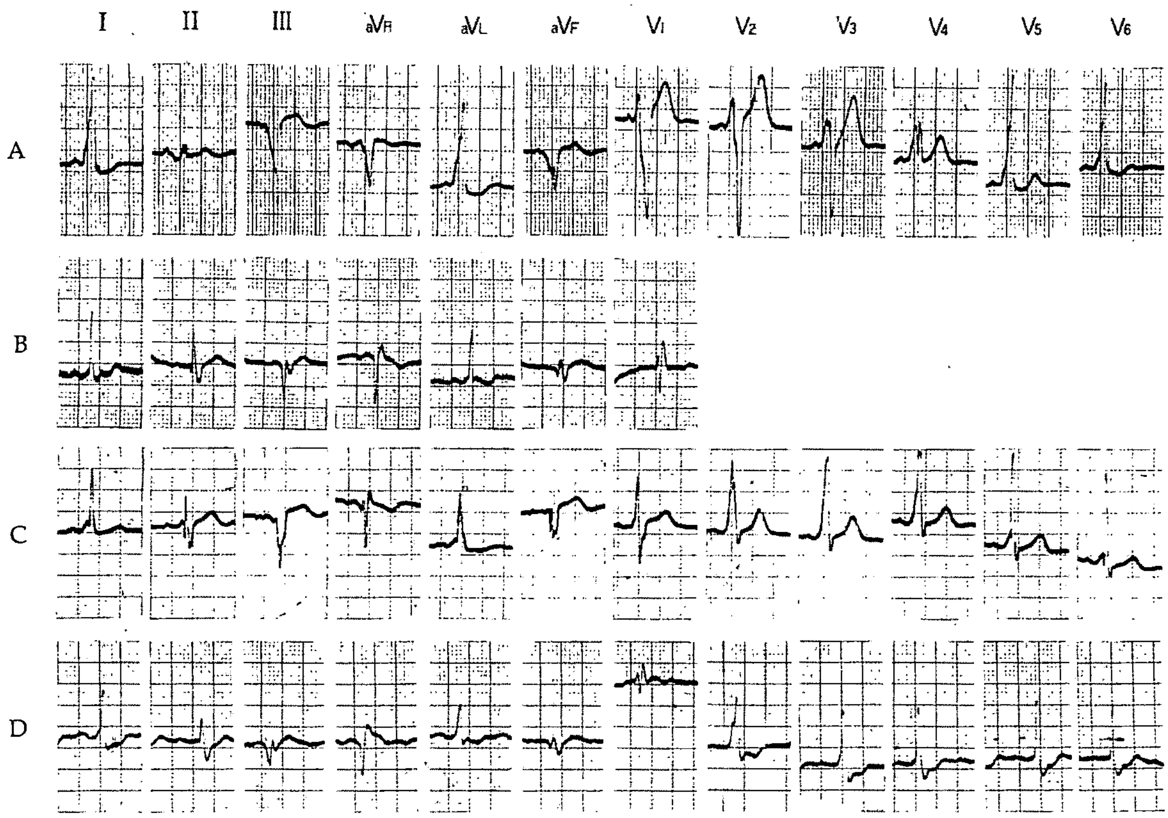

Fig 8. (Patient 5.) Electrocardiogram made (A) before the first operation, (B) 1 day postoperatively, (C) 10 days postoperatively, and (D) after the second operation. For details, see text.

Comment

There is no longer any doubt regarding the existence of multiple accessory conduction pathways in some patients with WPW syndrome. They have been observed in animals [1, 28], and several investigators have suggested that in humans with WPW syndrome in whom alternating type A and type B preexcitations are noted, multiple accessory conduction pathways may be present [22, 26, 27]. Anatomical [21, 25] and electrophysiological [3, 4, 7, 32] studies on humans have verified the existence of these multiple pathways, and surgical experiences with patients with WPW syndrome and multiple accessory conduction pathways also have been reported [16, 20, 30, 31].

A review of our 35 patients with WPW syndrome showed that in patients with only one accessory conduction pathway, neither the delta wave nor the tachycardia attacks recurred after successful interruption of the single pathway except in some patients seen early in the series [9]. All our patients in whom recurrence was noted had a second accessory conduction pathway. This observation differs entirely from reports that describe the failure of operation [2, 24], and contrary to these workers, we believe that, at present, the successful interruption of single accessory conduction pathways should present neither great technical difficulties nor recurrence. However, the preoperative or intraoperative detection of multiple accessory conduction pathways continues to present a challenge to the surgeon.

Possibilities for detecting multiple accessory conduction pathways preoperatively and intraoperatively are as follows:

1. Preoperative ECG
   a. Different delta waves
   b. Tachycardias of different rates
   c. Wider QRS interval during reciprocating tachycardia

2. Preoperative electrophysiological examinations
   a. Multiple preexcitation foci produced by atrial pacing at multiple sites
   b. Multiple preexcitation foci in endocardial mapping during ventricular pacing or reciprocating tachycardia
3. Intraoperative examinations
   a. Multiple preexcitation foci on epicardial mapping
   b. Multiple preexcitation foci on endocardial mapping under direct vision
   c. Provocation of reciprocating tachycardia by electrical stimulation after interrupting the first accessory conduction pathway.

In patients with WPW syndrome showing the typical ECG findings of alternating type A and type B preexcitations, there can be no doubt as to the existence of independent accessory conduction pathways in the left and right side of the heart, respectively. Furthermore, if two different types of fusion beat are present, multiple accessory conduction pathways should be suspected. However, if two pathways are located close to one another, it is difficult to discern them with ECG findings alone. In our series there were no instances in which ECG alone was useful in determining the presence of multiple pathways.

If two tachycardias with different rates are noted, the possibility exists that they are induced by different accessory conduction pathways [4]. Some cases have been reported in which the preoperative ECG during tachycardia showed the same pattern as that obtained during sinus rhythm except that the QRS pattern was wider during tachycardia [6]. We made this kind of observation in Patient 4. Previously, this phenomenon was thought to indicate that the stimulus descends in an anterograde fashion through the accessory conduction pathway to the ventricle and subsequently ascends retrograde through the normal conduction pathway, or, alternatively, that atrial flutter stimuli are conducted through the accessory conduction pathway to the ventricle at a 1:1 or 2:1 rate. However, if such a wide QRS pattern is noted during tachycardia, other considerations should be taken into account. One of these is the existence of multiple accessory conduction pathways. As far as concealed retrograde impulse conduction is concerned, as in Patient 4, endocardial mapping along the annulus of both the mitral and tricuspid valves will pinpoint the early excitation at the site of the accessory conduction pathway.

Electrophysiological study during atrial stimulation along the tricuspid annulus or coronary sinus is a valuable method for localizing the accessory conduction pathway in patients with WPW syndrome and a single pathway [8]. In this type of study, the time interval between the stimulus and the onset of the delta wave is measured. The point showing the shortest interval is closest to the pathway. When two separate points with short intervals are noted, this can be taken to indicate the presence of multiple accessory conduction pathways.

Further evidence for the existence of multiple accessory conduction pathways can be obtained from stimulation studies that show changes in the shape of the fusion wave. For instance, Gallagher and colleagues [7] reported patients with multiple pathways in whom the ECG showing type B preexcitation changed to type A when the left atrium was stimulated. Spurrell and associates [32] saw a patient in whom type B preexcitation during sinus rhythm changed to type A when a premature stimulus to induce supraventricular extrasystole was applied. In our Patients 3, 4, and 5, despite careful stimulation study, no such findings were obtained, thereby indicating that this method may not be successful in all patients with multiple accessory conduction pathways.

In all our patients, the retrograde atrial activation sequence was examined using a pickup electrode positioned in the coronary sinus or tricuspid annulus during reciprocating tachycardia or ventricular pacing. This method is indispensable in the detection of single accessory conduction pathways. If this examination detects a pathway other than the one demonstrated by routine electrophysiological examination, it confirms the existence of multiple pathways. However, we have not yet experienced this situation.

Intraoperative epicardial mapping is fundamental in the surgical repair of WPW syndrome. Gallagher and co-workers [7] encountered some patients with multiple accessory conduction pathways who showed two early activation areas upon epicardial mapping. However, we have not yet encountered instances of multiple early activation areas, although we consider ourselves proficient in the execution and interpretation of epicardial mapping and use a computer for the analysis of the activation sequence. For example, in Patients 1 and 3, we should never have missed the two separate early excitation areas if the two accessory conduction pathways had been functioning at the same time.

Last, endocardial mapping along the annulus by direct visualization under the beating heart condition after opening of the right or left atrium is another way to facilitate the detection of multiple accessory conduction pathways. In Patient 4, the second pathway was detected intraoperatively by this method. Even in left cardiac type WPW syndrome, this can be done by venting the left ventricle with a large vinyl tube inserted through the mitral orifice to avoid air emboli.

There are only a very few reports on the surgical interruption of multiple accessory conduction pathways. Gallagher and associates [7] reported some patients in whom the existence of multiple pathways was detected preoperatively and intraoperatively by means of their refined study. In the same year, Sealy, Gallagher, and Wallace [31] reported that among 50 operated patients with WPW syndrome, 6 were seen with multiple accessory conduction pathways. Three of these were successfully corrected, while in the remaining 3 patients the second pathway remained. We do not believe that we failed to detect the multiple pathways because of insufficient examination since we perform electrocardiophysiological studies routinely and extensively in many patients with arrhythmias, including those with WPW syndrome. Therefore, we are very well acquainted with these methods.

As possible explanations for our failure to detect the multiple accessory conduction pathways preoperatively or intraoperatively, we offer the following considerations: the second pathway may have been inert before the interruption of the first major pathway, becoming activated only thereafter; and the second, minor, pathway was not electrophysiologically manifested for some yet undetermined reasons. For instance, we have seen several patients in whom ECG showed type A and type B conversion alternatingly, or a normal and a fusion wave alternatingly. In these patients, the accessory conduction pathway was intermittently active and inactive. In our 4 patients who underwent a second operation and in whom the delta wave appeared 4 to 14 days after interruption of the first pathway, the second pathway was apparently inert preceding the appearance of the delta wave. It is highly unlikely that open-heart operation selectively depressed the function of the second pathway for such a long period.

Since the incidence of multiple accessory conduction pathways was as high as 14.3% (5 of 35) in our series, the possibility of the existence of these multiple pathways must be considered during preoperative examination and surgical repair of the WPW syndrome. We succeeded in the interruption of all ten multiple pathways, although a second operation was necessary in 4 of 5 patients. While Denes and colleagues [4] and Coumel and co-workers [3] regarded pessimistically the radical repair of WPW syndrome in patients with multiple pathways, the reports from the Duke group [7, 30, 31] and our present results encourage us to continue performing surgical repair of patients with multiple accessory conduction pathways in the WPW syndrome

Addendum

After submitting this paper, we saw another patient with multiple accessory conduction pathways. The patient was diagnosed preoperatively to have a major accessory pathway in the right lateral free wall and another concealed pathway in the left posterior free wall. Localization of the latter was diagnosed during the reciprocating tachycardia by an electrode catheter inserted in the coronary sinus. Both pathways were completely interrupted by one surgical intervention.

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Discussion

DR. WILL C. SEALY (Durham, NC): I appreciate being asked to discuss Professor Iwa's paper. Not only does he perform the operation for interruption of the Kent bundles, but he does all of the electrophysiological studies as well. That is a remarkable feat for a surgeon.

The experience at Duke includes 15 patients with multiple Kent bundles who were found among 160 patients operated on for arrhythmias resulting from Kent bundles. In 9 patients, the multiple pathways were found before operation by detailed electrophysiological studies. In 4 patients, the Kent bundles were found during intraoperative mapping. In 2 patients, however, the second pathway was found after operation. Thus, with accurate and detailed preoperative and intraoperative electrophysiological studies, 13 of the 15 patients had the multiple pathways demonstrated before attempted division.

Nearly all possible combinations of pathways were present. This included two pathways in one free wall in 3 patients and in 3 patients, a left free wall plus a posterior septal pathway. Among those of special interest were 6 patients with right free wall plus posterior septal pathways, 4 of whom had Ebstein's anomaly. Two patients had three pathways, 1 of whom had all the pathways identified by preoperative studies. In the other, the third pathway was found at operation.

Interruption of all of the pathways was successful in 12 patients who had twenty-five anomalous pathways. By election, three pathways in 3 patients with seven pathways were not interrupted. Two of the pathways were posterior septal in location but did not have the potential to cause death and were treated early in our experience. The other, in the left free wall, occurred in a patient with both a posterior septal and a right free wall pathway. The left free wall one would only conduct retrograde. Its potential for trouble was thought to be minor; therefore, opening the left atrium was not indicated.

Professor Iwa's contention that a second pathway may not become evident until a dominant first one has been divided happened in our experience with 3 patients. However, other factors can lead the surgeon to believe that this is so, when in fact it is not. For example, anterior septal pathways cause earliest ventricular activation over the infundibulum at some distance from the anomalous pathway. Unless mapping of the right atrium is done in tachycardia, one might suspect that the pathway is on the right free wall. One of Professor Iwa's patients had a right free wall pathway close to an anterior septal one. Posterior septal pathways also can be confusing for they, too, cause early ventricular activation at some distance from the pathway's crossing point from the atrium to the ventricle.

Mild trauma at operation and during electrophysiological study can temporarily block a pathway, thus interfering with its detection before and during operation. An atrial incision close to a Kent bundle may not only temporarily obtund its function at the first operation but will also alter the atrial activation sequence at the second operation, suggesting that the missed pathway at the first operation was a second one.

Kent bundles can be quite broad and have multiple strands. Lev and colleagues [1] described one in a patient with Ebstein's anomaly that measured 20 mm in width. A wide incision may be required to divide all the fibers.

In view of the chance that there is a hidden pathway adjacent to the known one, would Professor Iwa comment on whether or not this influences his decision about the extent of the incision in free wall pathways and in patients with Ebstein's anomaly?

Professor Iwa has handled this difficult problem unusually well. His methods and ours are so similar that I can but agree with almost all he has stated.

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DR. JOSEPH W. RUBIN (Augusta, GA): The authors have illustrated a very important aspect of WPW, namely the possible multiplicity of accessory pathways. Some second tracts may truly be unsuspected preoperatively because a much longer effective refractory period may cause masking; others may conduct preferentially anterograde or retrograde.

The instrumentation required for this type of operation is still developmental at the Medical College of Georgia but we have begun to perform surgical procedures for relief of paroxysmal supraventricular tachycardias associated with WPW.

The case report I will present for simplicity is straightforward. A 34-year-old man was troubled for fifteen years with paroxysmal supraventricular tachycardias and progressive disability, refractory to drugs. The ECG demonstrated a delta wave vector typical of lateral left ventricular preexcitation, which was confirmed by preoperative and intraoperative ECG mapping. The tract was easily located and divided, his symptoms ceased, and he returned to work. His ECG is normal.

Our latest patient was an 18-year-old man who had sustained "drop attacks" three or four times a day since infancy. These were finally ascribed to WPW with paroxysmal supraventricular tachycardias to 300 beats per minute or more. His accessory tracts were anteroseptal. He proved to have two pathways both very close and perhaps within the normal atrioventricular (AV) node–His bundle complex. Postoperatively, paroxysmal atrial tachycardia can be elicited by right ventricular pacing but electrically induced paroxysmal atrial tachycardia does not cause a corresponding increase in ventricular rate on repeated examination. Earliest atrial excitation is in the AV node region. The patient remains in sinus rhythm, and his syncopal attacks have ceased. Clearly he has a remaining pathway very close to the AV node–His bundle complex, which conducts retrograde from right ventricle to atrium.

Occasionally accessory anteroseptal tracts so close to the AV node–His bundle complex may only be treated by intentional destruction of normal AV conduction and subsequent permanent cardiac pacing. This case report also illustrates a point that Dr. Sealy has made succinctly in the past and today—that we require further insight into the technique of anatomical dissection of the septum in order to locate and divide aberrant conduction tracts without disturbing normal AV conduction. Congratulations to the authors for a fine presentation.

DR. IWA: I thank Dr. Sealy for his kind remarks. His experience and comments are very instructive to me at this time.

Wide incision, as Dr. Sealy suggested, may solve some problems of multiple accessory conduction pathways, but I just don't like to interrupt this fine, invisible structure without knowing where it is. We have an old proverb in my country. It says: "Don't use a big scimitar for cutting a small chicken."

We might be trying too hard to detect the precise location of the accessory conduction pathway in every instance. This experience, however, increased our knowledge of WPW syndrome, for example, the relationship between the ECG and the localization of the accessory conduction pathway, and a method of epicardial mapping.

Nevertheless, I agree with Dr. Sealy's proposition, and we now tend to make a bigger incision than before. Nevertheless, we know that a big incision on one side does not solve all the problems of multiple accessory conduction pathways. One of our 5 patients had pathways in bilateral sides of the heart.

Notice from the American Board of Thoracic Surgery

The American Board of Thoracic Surgery will give a voluntary recertification examination in the fall of 1981. Diplomates interested in participating in this examination should maintain a documented list of their cardiothoracic operations performed two years prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings and other continuing medical education activities for the two years prior to application for recertification.

A recertification brochure has been prepared outlining the rules and requirements. It also contains information about applying for the voluntary recertification examination. The brochure has been mailed to all Diplomates except those certified in 1979 and 1980. If you have not received yours and wish a brochure, please write the American Board of Thoracic Surgery, 14640 E Seven Mile Road, Detroit, MI 48205.

Descending Aortic Aneurysmectomy without Adjuncts to Avoid Ischemia

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ABSTRACT **Encouraged by reports on the safety of simple aortic cross-clamping for resection of descending aortic aneurysm, we began utilizing this technique more liberally in 1976. This study was undertaken to examine the results of operation in 36 patients, equally divided into two distinct groups.**

In Group 1, either extracorporeal circulation or indwelling temporary shunts were employed during the period of aortic occlusion. In Group 2, simple aortic cross-clamping was utilized to manage the lesion. No adjuncts were used to avoid ischemia in the latter group. The only 2 early deaths and two instances of paraplegia occurred in Group 1. In general, there were fewer complications in Group 2, with approximately two-thirds of the patients experiencing an uneventful postoperative course. These differences are considered important since the two groups were similar in respect to the extent and nature of the lesions and other factors contributing to operative risk.

Surgical management of lesions of the descending thoracic aorta of necessity require temporary cross-clamping of this major arterial pathway. Such interruption of arterial flow results in proximal hypertension and severe distal hypoperfusion. Left ventricular failure, spinal cord injury, and renal insufficiency constitute the most serious complications of this operation and occasionally lead to death. During the last two decades, various protective methods (bypass shunts with or without extracorporeal apparatus) have been utilized to minimize the deleterious effects of aortic cross-clamping. Although these measures have been useful in providing proximal decompression and reducing the ischemic damage to organs beyond the clamp, they have not been sufficient in eliminating the most dreaded complication, namely paraplegia. Furthermore, massive heparinization with its side-effects, and uncertainty regarding the adequacy of distal flow are added disadvantages of these techniques.

The knowledge that normothermic aortic cross-clamping for periods of at least 30 minutes without any adjuncts to avoid ischemia is well tolerated [6] and the excellent results reported with this technique by Crawford and Rubio [8] and others [1, 22] encouraged us to utilize this procedure more liberally in 1976. This clinical review was undertaken to evaluate the results of operation for lesions of the descending thoracic aorta, exclusive of acute dissection, employing this simplified technique.

Material

From 1973 through 1979, excisional therapy was employed in 36 patients with lesions of the thoracic aorta. Most were fusiform aneurysms arising distal to the left common carotid artery and terminating in the upper abdominal aorta. All patients had intact spinal cord function prior to operation. Based on the incorporation of one of the modalities employed to minimize the hemodynamic abnormalities associated with aortic clamping, the series is divided into two groups (Table).

Group 1

Group 1 (shunt group) consisted of 18 patients who had some type of adjunct incorporated in the operative procedure to provide proximal decompression and distal perfusion. There were 10 men and 8 women ranging from 18 to 69 years old (mean age, 46 years). The shunting method consisted of femoral vein–femoral artery bypass using a pump oxygenator in 12 patients, left atrium–femoral artery bypass using only a pump in 3, and temporary external shunt

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Comparative Analysis of Group 1 (Shunt) and Group 2 (No Shunt)

Variables	Group 1	Group 2
No. of patients	18	18
Age range (mean age) (yr)	18–69 (46)	20–82 (56)
Abdominal extension	1	3
Emergency operation	3	5
Early mortality	2	0
Paraplegia	2	0
Reoperation for bleeding	2	0
Uncomplicated course	7	13

using a Dacron graft or heparin-bound catheter (Gott shunt) in 3. Sixteen patients were seen with arteriosclerotic fusiform aneurysms (with only one extending into the upper abdominal aorta), and 2 had sustained traumatic rupture of the descending aorta in an automobile accident. These 2 and 1 patient with impending rupture of a large aneurysm were operated on under emergency conditions, while the remaining 15 patients had elective operation.

Paraplegia developed in 2 patients in this group. A 66-year-old woman whose aorta was clamped for nearly 100 minutes for resection of an extensive aneurysm had permanent paralysis of both legs. A 10 mm Dacron, temporary bypass graft was inserted to redirect the flow across the lesion. The second patient, a 48-year-old man who was totally paralyzed following the operation, has had partial recovery. Femoral vein–femoral artery bypass was employed in this patient, and he is the patient who needed emergency operation because of a rupturing large aneurysm. The aorta was clamped for 60 minutes, but following reconstruction there was a 10-minute period of severe hypotension requiring resuscitative measures. One other patient experienced weakness of the legs, which responded well to physical therapy.

There were 2 deaths in this group. A 21-year-old woman seen with total disruption of the proximal descending aorta caused by an automobile accident had a short tube graft interposed to reconstruct the damaged segment. Femoral vein–femoral artery bypass using a pump oxygenator was utilized during aortic occlusion. She required reoperation for bleeding on the first postoperative day, and although this was corrected, she died of rapidly progressive pulmonary insufficiency 48 hours after operation. The second patient, a 54-year-old woman for whom femoral vein–femoral artery partial cardiopulmonary bypass was employed died of complications arising from bleeding and hemorrhagic diathesis.

There were a number of other major complications in this group. Severe pulmonary insufficiency developed in 4 patients, 1 of whom required tracheostomy and another, prolonged endotracheal intubation. Renal failure occurred in 3 patients; only 1 of them had renal insufficiency preoperatively. Two patients experienced long-lasting hoarseness, and 2 required reoperation for bleeding. One of these latter 2 died. Only 7 patients enjoyed an uneventful postoperative course (see Table).

The only late death in this series involved a 68-year-old man who required replacement of the aortic valve and the ascending aorta 3 years after successful resection of the descending aortic aneurysm. His sudden and unexpected death, 4 months after cardiac operation, was presumed to have been caused by ventricular arrhythmias since postmortem examination was negative.

Group 2

Group 2 (no shunt group) also had 18 patients, most of whom underwent operation in the last 3 years of this study. The 12 men and 6 women ranged from 20 to 82 years old (mean age, 56 years). Simple technique of aortic cross-clamping was utilized in this group. In approximately two-thirds of the patients, it was necessary to use pharmacological agents immediately following the application of the clamp to control proximal hypertension. In the remaining patients, the systolic pressure did not exceed 200 mm Hg and no attempt was made to alter it. In only 2 patients was a Carlens endotracheal tube used to allow deflation of the left lung during most of the operation. Thirteen patients had elective and 5 had emergency operation. Of these 5, 3 were seen with traumatic rupture, 1 with aortobronchial fistula occurring 5 months after resection of a descending aneu-

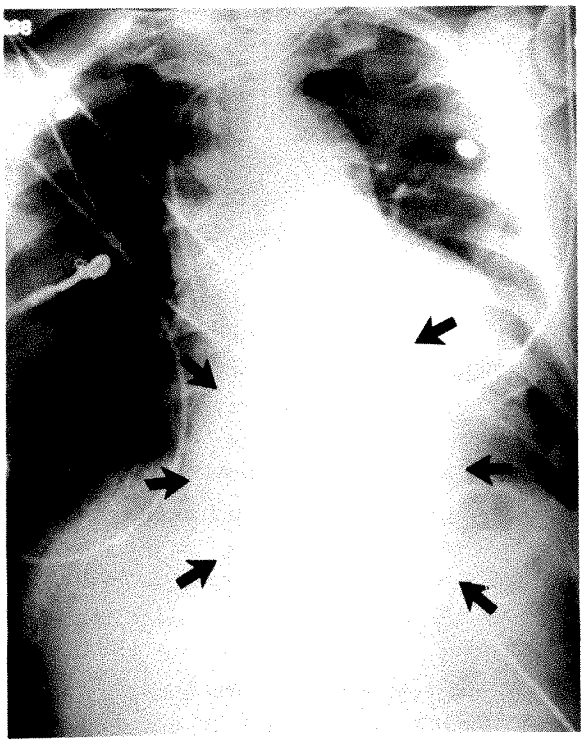

Fig 1. Chest roentgenogram of a 78-year-old man seen with a huge and painful thoracoabdominal aneurysm (outlined by the arrows) complicated by mediastinal compression and pericardial effusion.

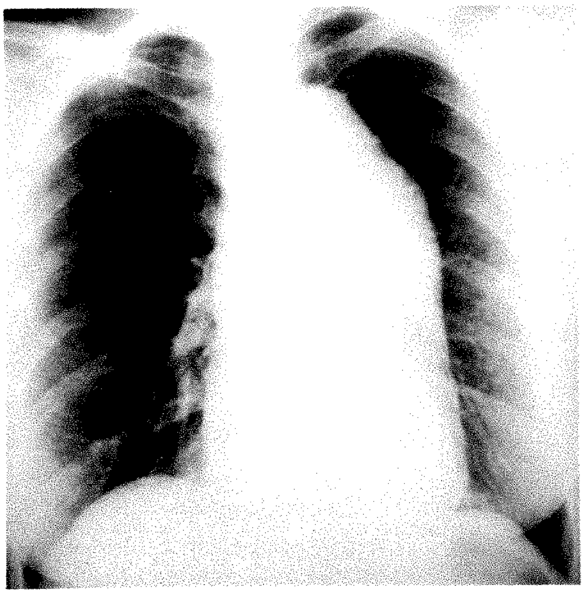

Fig 2. Chest roentgenogram of a 62-year-old woman seen with an aneurysm extending from the left subclavian to the superior mesenteric artery.

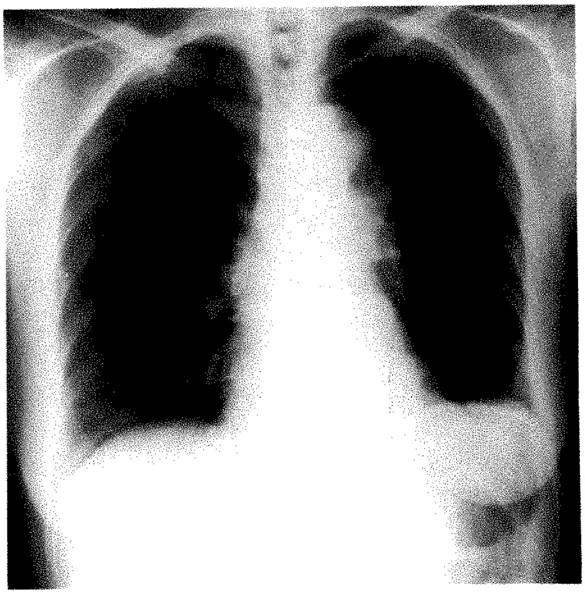

Fig 3. Chest roentgenogram of the same patient 4 years after replacement of the entire descending aorta and the upper abdominal aorta, and after celiac artery implantation.

rysm, and 1 with an extremely large, painful, and expanding aneurysm causing mediastinal compression and pericardial effusion (Fig 1). In 3 patients, the aneurysm extended into the abdominal aorta, and in 1 of these the celiac artery originated from the lesion and required transplantation to the side of the aortic graft (Figs 2, 3).

Based on the age range (5 patients 70 to 82 years old in this group as opposed to none in Group 1), the more extensive nature of the lesions, and the more frequent ominous clinical manifestations requiring emergency operation, Group 2 constituted a greater surgical challenge compared with Group 1. In spite of these increased risk factors, however, there were no deaths and no instances of paraplegia in Group 2. Transient weakness of the quadriceps muscles developed in 1 patient, which has left only minimal residual deficit. This patient sustained acute and total disruption of the proximal descending aorta in a motorcycle accident. The resulting false aneurysm was bleeding profusely into the pleural cavity when the chest was entered. Although the aorta was clamped for only 26 minutes, there was a period of severe hypotension following the release of the clamp even though this was done slowly and after blood loss had been adequately replaced.

The impressive observation in this group relates to the obviously fewer complications.

Much less blood transfusion was required during operation and none postoperatively. Two patients experienced hoarseness, and 3 had pulmonary complications, with 1 requiring tracheostomy and another, prolonged endotracheal intubation. Two patients (1 with preoperative renal insufficiency) experienced transient renal failure after operation. Thirteen patients, nearly twice as many as in Group 1, experienced an uneventful postoperative course (see Table).

The only late death in this series involved a 66-year-old man who had previously survived repair of a ruptured abdominal aortic aneurysm and later elective aneurysmectomy and graft replacement of the midportion of the descending thoracic aorta. He returned 5 months after the latter operation with left intrascapular pain and massive hemoptysis. Chest roentgenogram showed tremendous enlargement of the aorta at the site of the previous operation, and an aortogram strongly suggested disruption of the proximal suture line, with formation of a false aneurysm. At operation, the graft was found to be totally separated from the aorta proximally, was involved in a false aneurysm eroding into the lung, and was surrounded by a tremendous amount of pus. Cultures grew *Candida albicans*. After evacuation of the pus, debridement, and removal of the graft, a new graft was inserted under antibiotic coverage with amphotericin B.

The patient recovered, but returned several months later because of recurrent severe hemoptysis. At this time, all tests including bronchoscopy and aortogram were negative. He continued to do well, except for several additional transient episodes of moderate hemoptysis, each lasting a few hours and each carefully evaluated. The chest roentgenograms remained unchanged, and several additional bronchoscopies failed to disclose the source of bleeding. As part of this clinical review, posteroanterior and lateral chest roentgenograms were obtained recently (approximately 3 years after the second thoracic operation). The patient was asymptomatic and had not had any hemoptysis for the preceding several months. Ironically, however, two days after this examination, he died at home after an abrupt and exsanguinating hemoptysis. Postmortem examination showed disruption of the proximal anastomosis and what appeared to be an aortobronchial fistula.

The etiology of the aneurysm was similar in the two groups. Arteriosclerosis was the principal underlying pathological process. Total circumferential replacement was performed in all of these patients. There were no significant differences in the incidence of other cardiovascular disorders or clinical manifestations of ischemic heart disease in the two groups. Three patients in each group had previously had other arterial operative procedures—resection of an abdominal aortic aneurysm, carotid endarterectomy, and aortic bifurcation reconstruction for occlusive arterial disease.

In Group 1, with a shunt, the application of femoral vein–femoral artery bypass or the left atrium–femoral artery bypass was associated with a variety of difficulties, such as inadequate distal perfusion or labial proximal pressure sometimes to dangerously low levels. In Group 2, hypertension was easily controlled in every instance with pharmacological agents such as trimethaphan camsylate or nitroprusside, or by inhalation of either nitrous oxide or halothane.

Comment

The descending aorta is the most common location of a thoracic aneurysm, and most lesions are limited to the supradiaphragmatic aorta. The major complications of their repair include paraplegia, renal failure due to hypoperfusion of the spinal cord and kidneys, and acute left ventricular strain due to proximal hypertension. Various methods have been applied to avoid these problems, including utilization of extracorporeal circulation and temporary extravascular shunting. The first impressive series of thoracic aortic aneurysms in which left atrium–femoral artery bypass was employed to avoid distal ischemia was presented in 1958 by DeBakey and associates [9]. In their series of 36 patients, paraplegia developed in 2. Neville and associates [20] in 1968 reported no instances of distal organ damage following thoracic aortic operation in 19 surviving patients after using femoral vein–femoral artery bypass and a pump oxygenator. Bloodwell and colleagues [3] in 1968 reported development of partial paraplegia in 3 of 17 patients after the same technique had been employed. Kahn [16], using heparin-bound indwelling shunts to redirect the arterial flow around the lesion, encountered one instance of paraplegia in a series of 26 patients who had operation. Connolly and associates [6] in 1971 reported a series of 10 patients with descending thoracic aortic aneurysms who were treated by excision and graft replacement using tubing and an ingenious pumping device that did not require heparinization. This technique was employed during long periods of aortic clamping, and paraplegia developed in 1 patient.

The most impressive series of surgical treatment of aneurysms of the descending thoracic aorta was reported in 1978 by DeBakey and his associates [10]. Five hundred patients were in the series, and the lesions included arteriosclerotic aneurysms, aortic dissection, and traumatic rupture. There were 349 patients who underwent operation in which some type of shunt procedure was used to reduce proximal hypertension and provide distal perfusion during aortic cross-clamping. The more notable subgroup in this series was 117 patients operated on since 1970 in whom no shunts were employed. The authors reported lower operative mortality and no increase in the incidence of spinal cord ischemia or other complications associated with the latter technique.

Because of the complexities of extracorporeal circulation and in particular the need for high-dose heparinization, many surgeons are utilizing a polyvinyl catheter coated with tridodecylmethylammonium chloride (TDMAC) and bonded with heparin, advocated by Gott in 1972 [12]. In 1977, Lawrence and associates [18] reported the use of this shunt in the surgical management of 23 patients with descending thoracic aortic aneurysms. There were 2 deaths in their series, and paraplegia developed in a 20-year-old patient following the repair of a posttraumatic aneurysm. A 7.5 mm shunt was used, and it was postulated that the shunt may not have been sufficiently large to provide adequate distal flow. In a collective series of 365 patients [18], alternative techniques were employed, with an overall mortality of 13%. Among 188 patients with posttraumatic aneurysms, mortality was 6%, while among 177 patients with arteriosclerotic or dissecting aneurysms, mortality was 20%. Five instances of paraplegia were encountered. The incidence of paraplegia was higher in patients with traumatic aneurysms compared with those with chronic lesions. Paraplegia did occur in 2 of 26 patients in whom no shunts were employed. It appears that all reported series, with and without shunts, fail to establish statistically significant difference in the occurrence of paraplegia. This is probably due to the low incidence of this serious complication (1.3%).

The cause of acute paraplegia is probably related to both anatomical and physiological factors. Experimentally, simple cross-clamping of the aorta for periods longer than 30 minutes produces a high incidence of paraplegia [2, 21]. Division of the intercostal vessels adds to this incidence [5]. In a clinical analysis, however, Brewer and co-workers [4] found that this dreaded complication was not specifically related to aortic cross-clamp time, the number of intercostal vessels sacrificed, or the number of preexisting collaterals. Its sporadic and unpredictable occurrence when otherwise similar techniques are used may result from the anatomical variability of the blood supply of the spinal cord.

There is experimental and clinical evidence that clamping of the proximal descending aorta causing severe hypertension is associated with several unfavorable hemodynamic alterations that undoubtedly contribute to the outcome of operation. These include increased left ventricular end-diastolic pressure (LVEDP) and mitral insufficiency in dogs [14], and reduced cardiac output and an increase in pulmonary wedge pressure in man [17]. It is interesting to note that in the clinical study, insertion of an indwelling shunt helped return the systemic and wedge pressures to their baseline or preclamping levels, but failed to correct the low cardiac output [17].

In another study it was postulated that increased LVEDP results in elevated intramyocardial pressure, particularly in the subendocardium [23]. This, in turn, leads to subendocardial ischemia, which at least partially explains the impairment of left ventricular function during acute aortic occlusion. In anesthetized dogs with supravalvular aortic constriction, investigators observed relative underperfusion of the subendocardial left ventricular myocardium [23]. These changes, of course, would be accentuated in the presence of substantial coronary occlusive disease in man.

As stated by Crawford and Rubio in 1973 [8] and substantiated further by an accumulative experience published in 1979 [7], it would appear that to improve results, greater emphasis should be placed on elective operation prior to rupture, simplification of technique, preservation of cord circulation, expeditious operation, and prevention of hemorrhage and most importantly hypotension. The systemic blood pressure has been shown in animals to be the most important factor controlling blood flow to the spinal cord [11], and paraplegia has been observed in humans following episodes of hypotension [19]. The development of paraplegia, hours or days after a seemingly successful operation preceded by a period of hypotension, is quite suggestive of the important role that the level of blood pressure plays in the maintenance of adequate arterial flow to the spinal cord under these circumstances.

In chronic lesions, the number of sources of arterial supply to the spinal cord may be reduced by occlusion in the region of the disease and normal function may be maintained through the collateral channels. Such collateral circulation permits successful resection of the descending thoracic aneurysm in most cases since the cord is not dependent on the diseased segment for its blood supply. On the other hand, in acute processes such as acute dissection or trauma, time may not permit formation of collateral circulation and excisional therapy may interfere with cord circulation directly. Furthermore, acute aortic disease itself, such as dissection or thrombosis, may spontaneously produce paraplegia [13].

To simplify the techniques and expedite the operation, the graft is inserted in the generously opened aneurysm, making the proximal and distal anastomoses to the undivided aorta. The advantage of this method is the negligible dissection required, which minimizes injury to adjacent structures and preserves the collateral circulation. Closure of the sac of the aneurysm around the graft aids in achieving hemostasis while excluding the prosthesis from the neighboring structures [15].

Release of the aortic clamp and restoration of flow through the grafted segment demand particular attention. There are two important aspects to this maneuver, one related to a precipitous hypotension that may ensue, and the other to retention of air and possibility of subsequent air embolization. To ensure against air embolization, the segment between the clamps is filled with blood by a slight release of the proximal clamp. This is usually sufficient to displace the air. If necessary, however, one or two holes are made in the uppermost portion of the graft, using a 22 gauge needle. This allows for escape of any bubbles of air that may have been trapped in the grafted segment.

To prevent hypotension, several steps are taken simultaneously. Sodium bicarbonate is given to correct metabolic acidosis consequent to distal ischemia; provision is made for infusion of blood as fast as might be necessary; and most important, the flow is allowed through the grafted segment very slowly or intermittently while blood pressure is followed on the monitor. Sometimes it may take as long as 10 minutes before the clamp is removed and total aortic flow is permitted. Occasionally, it may be necessary to use a single dose of a vasopressor agent (for instance diluted Neo-Synephrine [phenylephrine hydrochloride]) to reverse the declamping hypotension.

With cautious encouragement based on the results of this study, we intend to continue to employ the simple method of aortic cross-clamping, without shunting, in surgical management of lesions of the descending thoracic aorta.

Addendum

Since the submission of this manuscript, we have operated on 4 additional patients using a simple method of aortic cross-clamping. Two patients had arteriosclerotic aneurysm, 1 had a chronic traumatic lesion, and 1 had acute aortic disruption, secondary to an automobile accident.

Two patients are of particular interest. A 69-year-old woman with an aneurysm of the descending aorta involving the subclavian artery underwent resection of the lesion with restoration of aortic continuity during a 32-minute period of aortic cross-clamping. The aorta was clamped proximal to the left subclavian artery. Upon the release of the clamp, copious bleeding was encountered from the posterior aspect of the proximal suture line. The bleeding was controlled manually, while distal flow through the graft was allowed. After several minutes, the aorta was reclamped, the graft was taken down, the proximal cuff was retailored, and a longer prosthesis was used to restore the flow. In spite of a second period of aortic cross-clamping of 27 minutes, the patient did not exhibit any neurological or ischemic damage postoperatively.

A 21-year-old man was seen with multiple fractures and near total disruption of the descending aorta, caused by an automobile accident. Although the aorta was clamped for only 37 minutes, he sustained a motor paraplegia following operation. Of the three unusually large intercostal arteries in the region of the tear, two were sutured and one was clamped during the repair. It was thought that these vessels were important sources of blood supply to the cord in this patient. In spite of an encouraging degree of improvement, the patient continues to have a major neurological deficit.

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Discussion

DR. VINCENT L. GOTT (Baltimore, MD): I appreciate the opportunity of being the primary discussant on this very excellent paper by Dr. Najafi and colleagues. Certainly, their results in the patients operated on without a bypass technique are excellent, and it would be hard to improve on them. However, I think that for the patient undergoing elective resection of a very large atherosclerotic aneurysm of the descending thoracic aorta, more protection can ordinarily be provided with some type of shunt around the aneurysm.

It is important to note that 15 of the 18 patients in the group receiving a shunt actually had pump bypass with systemic heparinization. I agree with Dr. Najafi that we ought to eliminate the use of pump bypass and systemic heparinization for these patients. Both of the deaths occurred in patients undergoing pump bypass, and death was related to substantial intraoperative and postoperative bleeding. These complications from systemic heparinization, of course, can be eliminated with the heparinized shunt. Incidentally, I now favor proximal cannulation in the apex of the left ventricle. It is simpler than cannulating the arch of the aorta or the subclavian artery.

As Dr. Najafi indicated, certainly in the experimental animal and very likely in the human patient, paraplegia can be minimized by maintenance of a reasonable blood pressure in the distal thoracic aorta. Lyman Brewer and others have studied this problem extensively and have pointed out that the anterior spinal artery is ordinarily not a continuous artery. There are usually three discontinuous segments in the cervical, thoracic, and lumbar areas. Because of this discontinuity in the anterior spinal artery and the fact that the thoracic portion is usually supplied by one major vessel from the eighth or ninth intercostal artery, it seems to make sense to reestablish flow by means of a shunt. On the other hand, paraplegia did develop in 2 patients in this series who had a shunt. Dr. Najafi indicated that these patients had large aneurysms with extensive resections, and it is possible that with an extensive resection and even with a shunt, a patient could have paraplegia if the intercostal artery is interrupted.

I am sure that Dr. Najafi would agree that the experience of the surgeon doing the operation makes a real difference. He referred to the excellent paper of Lawrence and co-workers who surveyed the members of the Samson Society 3 years ago regarding their experience with repair of aneurysms of the descending thoracic aorta. Of the 61 members who responded, only 26 had carried out operations for thoracic aneurysms. Nine of the 26 had performed 82% of the operations, and the remaining 17 surgeons had performed the operation only three and a half times per decade. This operation is not performed very frequently by most of us, and it probably does require a longer clamp time than in Dr. Najafi's hands.

In closing, I ask Dr. Najafi if there is any situation when operating on these patients in which he would use a shunt. Would he think that a shunt is of any benefit in the patient with poor ventricular function? Also, is there any duration of cross-clamping that would concern him?

DR. FRANCIS ROBICSEK (Charlotte, NC): I congratulate the authors for their beautiful clinical results and the outstanding presentation. It was evident to them and to many of us that the conventional method of using a different type of shunt certainly does not make the patient immune from either death from extensive dissection in surgical trauma or from spinal cord paralysis. While Dr. Najafi and his associates choose to proceed toward the radical method of Crawford, I choose to go back to the middle 1960s to the method of Dr. Hardy.

I simply put an end-to-side temporary permanent anastomosis to the aorta, then move the cross-clamp gradually down as I go down, and pick up the visceral branches one by one. I divide the aorta, do the distal anastomosis to the bifurcation or to the femoral arteries, oversew or ligate the aneurysm proximally, and leave the aneurysm itself inside the body. It later disappears. In my opinion, this method decreases the time of the operation and the necessity of extensive dissection. Also the aneurysm may stay open for a while and provide collateral circulation from one lumbar and intercostal artery to the other, and probably decreases the danger of a spinal cord paralysis.

In a control study of such a patient after this operation, the aorta was occluded and the graft in place a year later. A chest roentgenogram made 1½ years later showed the thoracic portion of the aneurysm, which was left in place. It had shrunk gradually and had practically disappeared. There was no pressure in the aneurysmal sac; thus, the aneurysm probably was completely thrombosed.

It is evident that the zero mortality and zero morbidity achieved in the present study cannot be improved on. But if we confront a patient with a thoracoabdominal aneurysm, those of us who probably do not possess the technical wizardry of Crawford and Najafi will find the Hardy method a very useful alternative to managing this very complicated disease.

DR. ALAN HILGENBERG (Denver, CO): I compliment Dr. Najafi on his presentation, which raises the question of which operative technique for descending aneurysm resection best protects the spinal cord and also remains simple and safe to use. With these points in mind, Dr. Rainer and I reviewed our experience with these aneurysms, all of which were done with either femoral-femoral bypass or the Gott shunt. Between 1965 and 1976, we performed 23 operations with femoral-femoral bypass and had no instances of paraplegia and 2 deaths (8.7%). Between 1976 and 1979, we used the Gott shunt in 11 aneurysm resections and had no paraplegia and 1 death (9%). This series of 34 consecutive patients demonstrates that the incidence of paraplegia can be very low when bypass or the Gott shunt is used routinely.

We believe that maintaining blood flow to the lower body and reducing cardiac afterload during aortic clamping is important.

I wonder whether the paraplegia in Dr. Najafi's series could be related to the location or extent of intercostal arteries sacrificed rather than to the method of spinal cord protection. I will be interested to see if the low incidence of paraplegia persists as Dr. Najafi's series of patients without shunts becomes larger.

DR. JOHN S. VASKO (Columbus, OH): We have always been reluctant to assume that the circulation is a bad thing and so have been reluctant to propose a technique that would seem to violate that principle. On the other hand, for the past several years I, too, have explored Dr. Crawford's concept of simple aortic occlusion in the repair of aneurysms. I have considered acute traumatic tears as an ultimate test because I believe that they probably provide the greatest index of whether or not an injury will occur to the spinal cord.

Prior to 1975 my associates and I had a larger series reported elsewhere, but since 1975 we have had 17 patients with acute traumatic ruptures of the thoracic aorta, with 1 death. In 12 patients, we simply cross-clamped the aorta and repaired them with a graft. The occlusion time for grafting ranged from 6 minutes to 45 minutes in 1 patient in whom the aorta had ruptured prior to the opening of the chest. The patient, who died, was a man who had a severe crush injury to the chest wall. It resulted in pneumonia and impaired pulmonary function.

Spinal cord injuries occurred in 2 patients. One was the patient who had preoperative rupture with hypotension, ventricular fibrillation, cardiac massage, and a 45-minute cross-clamp time. The other was a patient whose aorta was cross-clamped for 34 minutes. Also, two intercostal arteries were avulsed at the tenth thoracic level in the lower chest. They had to be repaired, and I believe this contributed to the occurrence of spinal cord injury.

DR. PANAGIOTIS N. SYMBAS (Atlanta, GA): I enjoyed very much Dr. Najafi's excellent presentation. Not being completely satisfied with either the femoral vein–femoral artery bypass or the external shunt during repair of descending aortic lesions, and having become somewhat puzzled with the difference in the experimental results obtained by various investigators and the clinical results obtained by Crawford, we investigated the hemodynamic, humoral, neural, and pathological and anatomical effect of cross-clamping the descending aorta in four groups of about 50 dogs. One group had femoral vein–femoral artery bypass, one had an external shunt, one had "pharmacological unloading" of the left ventricle, and one served as the control.

Since there is not enough time to elaborate on all of our findings, I will mention only the neurological effects. None of the dogs with femoral vein–femoral artery bypass or with an external temporary shunt had paraplegia, whereas 40% of the dogs treated with nitroprusside and 60% of the control dogs had paraplegia following 90 minutes of aortic cross-clamping. Since I have difficulty integrating Dr. Najafi's and Dr. Crawford's results with our results and those of other previous investigators, I will ask Dr. Najafi two questions. First, is it possible that the observed difference is related to the difference in species or to other factors that usually affect nonprospective clinical studies? Second, in view of the conflicting information available as to the safety of the various procedures during cross-clamping of the aorta, if paraplegia develops in a patient following an aortic procedure without any adjunct and if litigations are raised, which of the information available will prevail: the experimental or clinical?

DR. IVAN A. MAY (Oakland, CA): Dr. Najafi's results are certainly excellent. Roger Ecker and I would like to update a report made in 1976 of an alternative method of bypass which avoids heparinization and provides an unhurried aortic cross-clamp time. Using Wakabayashi's nonthrombogenic polyurethane polyvinyl graphite tubing without an oxygenator or heparin, we bypass through the groin from the right atrium to the femoral artery.

The patient is put in the right lateral decubitus position with the left leg pulled back to allow isolation of the femoral vein and artery while the chest is being opened. A catheter is passed to the right atrium through the femoral vein. This mixed venous blood is propelled by a rotary pump to the femoral artery.

Bypass perfusion averages 1,500 to 2,000 ml per minute, which helps control proximal hypertension and provides adequate distal perfusion. One hundred percent oxygen for ventilation during aortic cross-clamp time assures adequate oxygenation of the distal perfusate. Average cross-clamp time has been 45 minutes.

We have used this technique in 28 patients, including 8 with traumatic ruptures and 7 with type III dissecting aneurysms of the aorta. The only deaths have been 2 patients with dissecting aneurysms, which ruptured hours or days later. There have been no other complications.

We find this method very satisfactory and continue to use it.

DR. NAJAFI: I certainly thank the discussants and acknowledge the valuable contributions they have made to the subject in general and to this presentation in particular. Several questions were asked, and I will try to answer them briefly.

Dr. Gott asked if we would consider using a shunt. The answer of course is yes, and we have them available in our operating rooms because there are instances when we may have to deviate from the simple method of cross-clamping. His second question related to aortic occlusion time and its relationship to the incidence of spinal cord injury. I have no question in my mind that time is a factor even though in the literature it has been underestimated by those who use this technique. I think that if aortic cross-clamp time exceeds 60 minutes, regardless of other circumstances, a neurological deficit is more likely to develop. Therefore it is important to carry out the operation as expeditiously as possible.

Dr. Robicsek's modification—performing a proximal end-to-side anastomosis or, if the aorta is available beyond the lesion, doing the distal anastomosis first in an end-to-side fashion—is one that has been occasionally employed. In fact, the patient who had the shortest duration of aortic cross-clamping in our series, which was about 16 minutes, was done by my colleague, Dr. Serry, who used exactly the same technique as Dr. Robicsek.

The next question related to the number of intercostal arteries divided and whether the 2 patients who had paraplegia in the shunt group had more intercostal arteries sacrificed. I can say with certainty that this was not the case, because in both patients laminated thrombi had already thrombosed most of the intercostal vessels. These 2 patients did have extensive aneurysms. In 1 the aorta was clamped for 60 minutes and in the other for 90 minutes because of certain intraoperative complications, and I am sure the duration of aortic occlusion contributed to the paraplegia.

Dr. Symbas asked whether or not laboratory species influence the outcome of research on spinal cord injury. I believe the dog is an unsuitable animal on which to try to do investigative neurological work, extrapolate conclusions, and apply them to humans. In terms of litigation, both techniques of aortic cross-clamping and shunting are open to scrutiny as to their relationship with distal ischemic complications.

Finally, I will impart some advice particularly to our younger colleagues. Since paraplegia is the most dreaded complication and since it occurs with every conceivable technique employed, it is absolutely mandatory to gently but very explicitly inform the patient and the family of this potential tragedy prior to the operation. This will prevent unnecessary anguish that is associated with the patient not having been sufficiently informed and is likely to eliminate the source of litigation.

Notice from the Southern Thoracic Surgical Association

The Twenty-seventh Annual Meeting of the Southern Thoracic Surgical Association will be held at The Greenbrier, White Sulphur Springs, WV, Nov 13–15, 1980. There will be a $100.00 registration fee for nonmember physicians except for guest speakers, authors and co-authors on the program, and residents. There will be a Postgraduate Program on Selected Operations by Experts. This meeting has been approved for Category I, 14 hours CME credit.

Manuscripts of papers accepted for the program must be submitted to *The Annals of Thoracic Surgery* by October 15, 1980.

Hotel reservations are sent to members. Guests may correspond with The Greenbrier, White Sulphur Springs, WV 24986. (Phone: (304) 536-1110.)

Richard B. McElvein, M.D.
Secretary-Treasurer

Further Evaluation of the Circular Sequential Vein Graft Technique of Coronary Artery Bypass

Joseph C. Cleveland, M.D., Ira M. Lebenson, M.D.,
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Daniel B. Nelson, M.D., Raymond J. Suchor, M.D.,
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and John R. Dague, B.S.N.

ABSTRACT **Our study reports a series of circular sequential vein grafts in 21 patients with highly symptomatic triple-vessel coronary artery disease. Four or more distal anastomoses were done in each patient. Thirteen of the patients were restudied, and the results revealed a 97% patency rate for distal anastomoses (58 out of 60) at 4 to 13 months after operation. One patient died 2 months after operation. Postmortem examination revealed a desmoplastic, fibrotic reaction at the proximal anastomosis of the circular graft, with 3 of 4 distal anastomoses patent. Twenty of the 21 patients in this series are now alive with asymptomatic cardiac status 14 to 22 months after operation.**

The finding by Grondin and associates [1] of increased patency rate with this technique for distal anastomoses is confirmed. The circular sequential vein graft represents a particularly advantageous technique for patients in whom 4 to 6 distal anastomoses are needed for complete revascularization and in whom one or more vessels have limited runoff. The obvious disadvantage of this technique is that all distal anastomoses depend on a single proximal anastomosis.

There is virtually no debate that coronary artery bypass operation ameliorates the symptoms of angina pectoris in the vast majority of patients [2, 3]. Hurst and co-workers [3] concluded that "we have adequate evidence that bypass surgery prolongs the life of patients with left main arterial obstruction and triple or double vessel obstruction." Additionally, it has been shown that exercise-induced myocardial dysfunction is usually abolished [4]. Relief of symptoms and adequacy of myocardial revascularization are related to graft patency [5]. Various studies have demonstrated saphenous vein patency to range between 75 and 90% in the first 6 to 12 months following operation [2, 4, 6].

Since the advent of coronary artery bypass operation, multiple techniques have been used and advocated. In the last two or three years, bypass to smaller branches of the coronary tree, as well as the major trunks, has been practiced. Thus, complete or total myocardial revascularization and high patency rates of the bypass conduits are key technical points of this operation. The experience reported by Grondin and colleagues [1] with the circular sequential vein graft seemed to achieve these goals with four to five distal vessels being bypassed per patient and a reported patency of 96%.

In February, 1978, we began to use the circular sequential saphenous vein bypass graft technique on selected patients with symptomatic triple-vessel coronary artery disease (Fig 1). Twenty-one such patients underwent operation during 1978, and 4 to 6 distal anastomoses were constructed in each. One patient died 2 months after operation, and postmortem examination showed severe scarring and near occlusion of the proximal anastomosis, even though 3 of 4 distal anastomoses were patent. After this event, the remaining 20 were contacted and angiographic restudy was recommended. Thirteen patients were restudied.

Material and Method

The 21 patients ranged from 37 to 73 years old (mean age, 57 years). There were 19 men and 2

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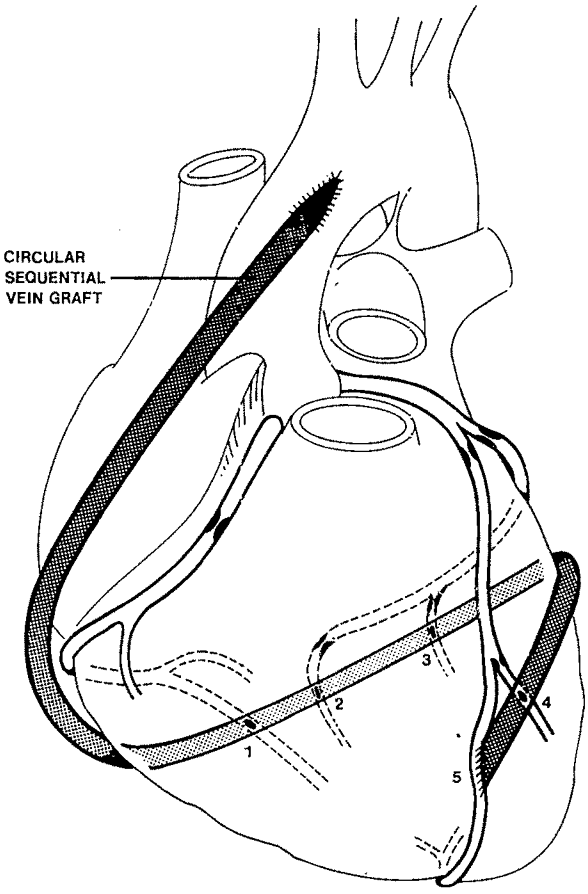

Fig 1. Circular sequential saphenous vein graft with distal anastomoses to (1) the posterior descending right coronary artery, (2) the second marginal circumflex and (3) the first marginal circumflex coronary arteries, (4) the diagonal branch, and (5) the left anterior descending coronary artery.

women. All had severe triple-vessel coronary artery disease with disabling angina. Eight patients had unstable angina, i.e., unprovoked angina, or an accelerating pattern in terms of frequency and severity. Four patients had left main coronary artery disease (stenosis greater than 70%). All except 2 of these patients were on a regimen of maximal medical therapy at the time operation was advised. In every patient, there was some distal vessel atherosclerotic disease and less than ideal size in one or more arteries to be grafted.

All of the patients were operated on using standard cardiopulmonary bypass techniques with moderate hypothermia and hemodilution. Myocardial protection was accomplished with cold cardioplegic solution infused into the aortic root to achieve electromechanical rest of the myocardium. The distal anastomoses were done first in the following sequence: An end-to-side anastomosis was created on the left anterior descending coronary artery. The anastomosis was usually about 6 mm in length, and the largest segment of the reversed, trimmed, and spatulated saphenous vein was used. The next coronary arteries to be grafted were one or more diagonal branches. These were side-to-side anastomoses with a 3.5 mm opening in the diagonal coronary artery and a 3.5 mm oblique opening in the saphenous vein. For the circumflex marginal coronary arteries, a vertical 3.5 mm opening in the coronary artery and a 3.5 mm transverse opening in the saphenous vein were made. Again, a side-to-side anastomosis was created. Usually the posterior descending aspect of the right coronary artery was used for anastomosis, and a vertical opening was made here and an oblique or vertical opening in the saphenous vein, again 3.5 mm in length. The final anastomosis was made to the highest anterior part of the ascending aorta near the middle of that structure. It was done in a vertical manner and was about 7 mm long.

This technique varies from the technique described by Grondin and co-workers [1] in that we did not use the diamond shaped side-to-side anastomosis or start at the same point on the heart. All coronary anastomoses were gently probed with 1 mm, malleable, metallic probes prior to completion to make sure that both proximal and distal anastomoses were patent. A continuous suture technique was used in all anastomoses with 7-0 polypropylene cardiovascular suture for distal anastomoses and 5-0 polypropylene cardiovascular suture for proximal anastomoses. A two-needle technique was employed with tying of the single suture at the midpoint of the second side of the anastomosis. This particular technique has been used by our group for all coronary anastomoses and has been shown to be quite satisfactory on numerous reexaminations.

Results

Tables 1 and 2 show the important data for the entire patient group. Flow rates in the vein grafts were measured with an electronic flowmeter just beyond the aortic anastomosis,

Table 1. Preoperative and Postoperative Data on the 13 Patients Who Underwent Recatheterization

Patient No.	Age (yr)	Disabling Angina	Unstable Angina	Left Main Coronary Artery Disease[a]	Preop Functional Class (NYHA)	Preop Systolic Ejection Fraction (%)
1	71	+	+	−	3	48
2	58	+	+	−	3	42
3	51	+	−	−	2	58
4	53	+	+	−	3	42
5	69	+	−	+	3	51
6	66	+	−	+	2	23
7	38	+	−	−	3	43
8	63	+	−	−	3	54
9	58	+	−	−	3	50
10	58	+	−	−	2	71
11	37	+	+	−	3	62
12	62	+	−	+	3	80
13	53	+	−	−	3	66

[a]Greater than 70% stenosis.
NYHA = New York Heart Association.

prior to chest closure. The range was from 100 to 400 ml per minute (mean, 197 ml per minute).

There was a zero operative mortality for this series, and a single late death occurred at 2 months. This patient was readmitted to the hospital because of chest pain and died shortly after readmission. Postmortem examination revealed a severe, fibrotic, desmoplastic reaction of the proximal anastomosis of the vein graft and aorta. Three of 4 distal anastomoses were patent.

That finding prompted a restudy of the remaining patients. All were contacted and asked to undergo reevaluation by clinical examination and cardiac recatheterization. Six patients declined angiographic restudy. All had an asymptomatic cardiac status. They did submit to clinical reexamination and were found to be in New York Heart Association Functional Class I. One patient agreed to the restudy, but severe hives had developed at his first cardiac catheterization. Because he was extremely active and asymptomatic, it was thought the risk of recatheterization exceeded the benefits to be gained.

The remaining 13 patients were restudied between 4 and 13 months after operation (mean, 8 months). Eleven were completely asymptomatic and active. One patient had been very active but mild recurrent angina was developing on heavy exertion. Restudy of this patient showed a 95% proximal stenosis of the sequential vein graft. This patient was promptly reoperated on, and a saphenous vein bypass to the previous bypass graft was constructed. Now, he is again very active and completely asymptomatic. Another patient was admitted to the hospital with anxiety and chest wall complaints. The graft was patent despite widespread diffuse disease of all coronary arteries. Twenty of the 21 patients are alive and essentially asymptomatic in terms of cardiac status 14 to 22 months following operation.

In the 13 patients who underwent recatheterization, there were 60 distal anastomoses, 58 of which were patent at the time of recatheterization. Two patients each had a single marginal coronary artery of small size which could not be refilled at the time of repeat injection of the sequential circular graft. This is a 97% distal patency rate. With the additional information gained at postmortem examination of the 1 patient who died, the distal patency rate becomes 61 of 64 (95%). Systolic ejection fractions were slightly increased postoperatively but were not significantly different from

No. of Anastomoses	Flow in Grafts (ml/min)	No. of Grafts Patent on Restudy	Postop Systolic Ejection Fraction (%)	Time to Restudy (mo)	Postop Functional Class (NYHA)
5	250	4	61	13	1
5	150	5	46	10	1
5	310	5	62	10	1
5	130	4	48	9	1
5	290	5	67	8	1
4	270	4	36	11	1
4	180	4	47	4	1
4	140	4	49	8	1
4	220	4	51	6	1
5	180	5	66	6	1
4	165	4	48	8	1
5	135	5	77	4	1
5	130	5	64	8	1

Table 2. Data on the 8 Other Patients in the Study

Patient No.	Age (yr)	Disabling Angina	Unstable Angina	Left[a] Main Coronary Artery Disease	Preop Functional Class (NYHA)	Preop Systolic Ejection Fraction (%)	No. of Anastomoses	Flow in Grafts (ml/min)	Postop Functional Class (NYHA)
1	45	+	+	−	3	51	5	150	1
2	59	+	+	−	2	55	4	140	1
3	48	+	−	−	3	67	5	N.A.	1
4	55	+	−	−	3	60	6	200	1
5	50	+	+	−	4	49	5	250	1
6	69	+	+	−	3	43	5	150	1
7	65	+	−	−	3	70	4	400	1
8	73[b]	+	−	+	3	61	4	100	1

[a] Greater than 70% stenosis.
[b] This was the patient who died 2 months after operation.
NYHA = New York Heart Association.

preoperative values ($p > 0.05$). There was a mean systolic ejection fraction of 53% preoperatively, and the mean ejection fraction postoperatively was 56%. All of the proximal anastomoses in the remaining 12 patients studied were widely patent.

Comment

The most salient finding of our study is the confirmation of a distal anastomotic patency rate of about 96% as reported by Grondin and co-workers [1]. Their patients were restudied within six weeks after operation. Our patients were restudied at a mean of 8 months after operation. Thus, the immediate and intermediate distal patency rate of about 96% in such a group of surgical patients is demonstrated and confirmed. Flow rate is a major factor in short-term and long-term patency rates of vein grafts. Further, patency rate and completeness of myocardial revascularization are major determinants of successful long-term surgical results. Thus, the circular sequential graft meets these requirements for myocardial revascularization quite well.

The problem of the dependency of all distal anastomoses on one proximal connection was demonstrated in our series. We believe that in both patients who had stenosis of the proximal anastomosis, the problems were due to technical considerations that can be resolved and that are not inherent weaknesses of the method. The patient who died was the eldest patient in the series (73 years old). The aorta was highly atherosclerotic with a concomitant inflammatory response. To try to avoid an area of heavy plaque formation, we shifted the proximal anastomosis to the right side of the aorta rather than place it in the usual position (anterior aorta). The saphenous vein was also somewhat small compared with a usual-sized vein. Placing a large vein patch on the aorta and the circular graft into this vein patch with the use of a larger segment of saphenous vein (necessitating a splice) might have prevented the problem that later developed.

In the second patient with difficulty, the saphenous vein bifurcated (going distad) just above the knee into two equal-sized vessels. This meant that the proximal anastomosis would have only a marginal size. A larger vein used proximally (by means of a splice) would have been preferable. The situation was later repaired with the saphenous vein from the opposite leg as a new bypass to the existing graft using a large segment for a proximal generous cobrahead anastomosis.

Although our surgical technique differs somewhat from that described by Grondin and colleagues [1], we find only one difference that we consider crucial. They stated that the arteriotomies for the side-to-side anastomoses should be 4 to 6 mm in length. We find that a 3.5 mm opening is appropriate, but that more than 4 mm will always consume so much surface area of the vein that it will "pucker in" the saphenous vein, thereby creating a potential obstruction to flow. Recently a vein patch angioplasty was necessary when the arteriotomy for a side-to-side anastomosis was inadvertently extended to 5 mm. This puckered in too much of the remaining saphenous vein, and repair was done by placing a large diamond-shaped vein patch on the opposite side. Other than that, we think that either technique is satisfactory for construction of the circular graft. In any event, the circular sequential graft is technically more demanding than the usual double or triple bypass using single veins.

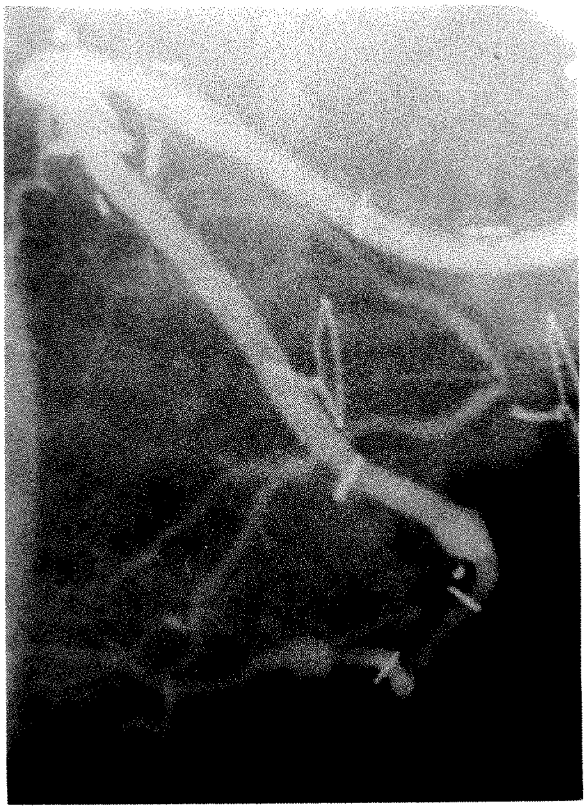

Fig 2. Angiogram made at restudy of a patient with a circular sequential saphenous vein graft. The distal vessels bypassed as well as the course of the saphenous vein are demonstrated.

We certainly recommend that patients be carefully selected for circular sequential grafts. Probably no more than 15% of patients having coronary bypass operation are suitable candidates. We consider patients who have the most advanced degree of coronary artery disease to be the most suitable for this technique (we recognize that no patient is truly inoperable). Even if the coronary anatomy is as described but the saphenous vein is not of good size and character, other techniques will be more appropriate. However, there exists a subgroup of patients who seem to be ideal for this technique. They are highly symptomatic patients with triple-vessel coronary artery disease, with or without left main involvement, who need four to six distal vessels bypassed to achieve adequate to complete myocardial revascularization. The functioning of a good circular graft is impressive in seeing and stripping the graft at operation, measurement of the flow rate in the graft at operation, and visualization of the graft on repeat angiography (Fig 2). Our study confirms the early patency rate of 96% obtained by Grondin and co-workers [1] and demonstrates that this rate is present up to 13 months after operation. We know that grafts patent at one year stay patent and functioning for upwards of seven years [7].

We believe that all patients in whom this technique of myocardial revascularization is used should be studied by repeat coronary and graft arteriography within 6 months after operation until the results of the technique are more firmly established. Potential problems can be identified and corrected by this approach. As in most surgical endeavors, problems tend to lessen with experience as results improve.

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Discussion

DR. CLAUDE M. GRONDIN (Montreal, Que, Canada): The number of patients and the patency rate reported by Dr. Cleveland are similar to what my colleagues and I reported three years ago. There are some differences, however..

We did not encounter stenosis on the proximal graft, which Dr. Cleveland attributes to a faulty technique. I am concerned that in his series there were two instances of severe narrowing of the proximal portion of the graft, one said to be of 95%. These, of course, endanger patency of all the distal anastomoses. Therefore, the reported 96% patency rate may be misleading if this is not taken into account.

The second point of difference is in the occurrence of isolated occlusion of a side-to-side anastomosis without concomitant occlusion of the graft beyond such an occlusion. We did not see this phenomenon. I relate it to the use of parallel side-to-side anastomoses instead of diamond side-to-side anastomosis, as described in our series.

We believe there are some important technical points in a circular vein graft. The thigh vein should be used. It is important to measure the distance between anastomoses before clamping the aorta and to use diamond side-to-side anastomoses. At times it may be necessary to use an additional segment of graft from the aorta to the primary graft.

Like Dr. Cleveland and his group, we have been concerned with the risk of having all the distal 4 or 5 anastomoses depend on a single aortic orifice. Therefore, recently, particularly in instances when the segment of graft next to the aorta is of small caliber or when there is any doubt concerning excess length or kinks, we have used a segment of graft between the aorta and that segment of the graft comprised between the left arterior descending coronary artery and the first diagonal branch. This anastomosis, by the way, must be on the medial aspect of the primary graft because of the danger of adding too much height to that graft. This could lead to compression and occlusion of the secondary graft.

DR. LEBENSON: Thank you, Dr. Grondin, for your comments. Our problems with the proximal anastomoses were encountered early in our experience (the steep portion of our learning curve). We believe now that we have overcome these technical problems.

We certainly appreciated your comments about the additional graft and will take that into consideration. We are comfortable in performing side-to-side anastomoses in any configuration that is comfortable for us. As the patency rates for all techniques appear to be equal, we will probably continue doing what seems most convenient and comfortable for us.

We stopped performing the circular grafts while we restudied the patients. Since the results were satisfactory, we performed this operation in an additional 15 patients, all of whom are asymptomatic at this time.

Myocardial Protection Through Cold Cardioplegia Using Diltiazem, a Calcium Channel Blocker

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and Claude M. Grondin, M.D.

ABSTRACT **During two hours of aortic clamping, two groups of 10 dogs each were given an intermittent infusion of a cold solution in the aortic root. In one group, the solution contained 20 mEq per liter of potassium chloride (KCl) and in the other, a calcium channel blocker (diltiazem). Left ventricular (LV) performance was measured by calculation of LV pressure, left ventricular end-diastolic pressure (LVEDP), cardiac index (CI), and stroke-work index (SWI). Regional myocardial function was assessed through ultrasonic crystals implanted in the subendocardial areas of both the left anterior descending (LAD) and circumflex coronary arteries.**

Dogs receiving KCl displayed deterioration of LV performance as evidenced by a return of maximal LV pressure, maximal rate of rise of LV pressure (dP/dt_{max}), CI, and SWI to 74 ± 4%, 87 ± 5%, 74 ± 6%, and 59 ± 6%, respectively, of the initial (before clamping) values. Animals that received diltiazem, on the other hand, had for the same variables a return to 85 ± 4%, 99 ± 7%, 129 ± 8%, and 111 ± 10% of the initial values. The rate of relaxation (peak negative dP/dt) decreased in both groups but less in dogs receiving diltiazem. Regional function in the area of the LAD and circumflex arteries showed little change in either group.

We conclude that cold cardioplegia with a solution containing KCl or diltiazem protects the myocardium during prolonged ischemic cardiac arrest. Return of LV function on the whole is superior when diltiazem is used.

Despite the numerous experimental [7, 9, 13, 14, 19, 26, 29] and clinical [3, 5, 9] studies confirming the protective effect of hypothermia combined with membranoplegia during ischemic cardiac arrest, there continues to be some doubt [4, 6, 17, 27] on the efficacy of this method of myocardial protection, particularly when potassium chloride (KCl) is used as the cardioplegic agent. Although the ideal solution has yet to be found, studies in several laboratories have led to important changes in the basic formula [9, 14, 15]. Calcium channel blockers, for instance, are known to paralyze myocardial activity [8] and reduce reperfusion injury [2, 28, 31]. Recent reports on the experimental use of two of these agents to limit reperfusion injury have been encouraging [2, 21, 22, 25].

The present study was designed to compare the efficacy of two cold solutions in protecting the myocardium during prolonged ischemic cardiac arrest in the dog. One contained KCl and the other, diltiazem, a new anticalcic agent.

Material and Methods

Twenty mongrel dogs weighing from 23 to 30 kg were anesthetized with sodium pentobarbital (30 mg per kilogram of body weight at induction, with additional boluses of 130 mg as needed). Following intubation and ambient air ventilation with a volumetric respirator (Harvard type 34 RH), the heart was exposed through a left thoracotomy. Polyethylene catheters were placed in the left carotid artery, the left internal jugular vein, and the left femoral vessels for monitoring of pressures (Statham P23Db manometers), cardiac output measurement, blood sampling, and administration of drugs. The left ventricular (LV) apex was cannulated and linked to a manometer or to a venting system during cardiopulmonary bypass (CPB) Two pairs of ultrasonic crystals* were implanted in the subendocardial layers of

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the myocardium, one in the area of the left anterior descending coronary artery (LAD) and the other in the area of the circumflex artery and hooked to a sonomicrometric system* [16, 30]. Ventricular septal temperature was monitored through a thermoresistant needle (Yellow Springs Instrument) and systemic temperature, through a rectal probe. The electrocardiographic tracing was recorded through peripheral leads.

Following systemic heparinization (3 mg per kilogram), CPB (Travenol pump and bubble oxygenator model 5 MO 314) was instituted through cannulation of the right atrium and the right femoral artery. Hemodilution was used with a prime of two-thirds Ringer's lactate solution, one-third dextran, and 44 mEq of sodium bicarbonate, adjusted to body weight (50 ml per kilogram). Hematocrit was near 20% (20 ± 4%). Perfusion flow was kept around 75 ml per kilogram and regulated so as to maintain mean aortic pressure at 50 mm Hg. Arterial pH during CPB was kept at 7.40 ± 0.5. Under total bypass, with the left ventricle decompressed and systemic temperature lowered to 22° to 24°C, the ascending aorta was clamped. Immediately following clamping, 200 ml of a cold cardioplegic solution (4°C) was injected in the aortic root using a pressure of 120 to 130 mm Hg,* and the heart was immersed in cold saline solution (4°C). Reinjection of 100 ml in the aortic root and reimmersion of the heart in cold saline solution were repeated after 30, 60, and 90 minutes of clamping. This kept septal temperature below 18°C.

After two hours, the aorta was unclamped and rewarming began. During rewarming, the heart was defibrillated as soon as possible and paced when needed. The LV apex was decompressed and the aortic pressure maintained around 70 mm Hg. After 30 minutes of reperfusion and rewarming, CPB was discontinued. Hemodynamic stability was achieved through transfusion of the perfusion fluid (left ventricular end-diastolic pressure [LVEDP] kept between 5 and 12 mm Hg). No drugs that could stimulate or depress myocardial action were administered during the experiment.

Two groups of 10 dogs were studied. In Group 1, 20 mEq of KCl was added to the cardioplegic solution. In Group 2, diltiazem, 150 μg per kilogram, was added to the basic solution, which consisted of Ringer's lactate solution in 5% dextrose in water, sodium bicarbonate (18 mEq per liter), and mannitol (22.2 gm per liter); osmolarity, ± 600 mOsm per liter; pH 7.7. In this second group, a bolus of 15 μg per kilogram (± 3 ml of liquid at room temperature) of diltiazem was placed in the aortic root just before unclamping so that the anticalcic agent could reach the myocardium with the onset of reperfusion (most of the structural damage is said to occur during the first few minutes of reperfusion [20]).

Measurements

BEFORE CLAMPING. Prior to the institution of CPB, the electrocardiogram and LVEDP were recorded on a Gould apparatus (Brusch, model 2400). Aortic pressure, central venous pressure, LV pressure and its first derivative dP/dt, and the sonomicrometric signals and their derivatives were recorded on a Beckman model R411 recorder. Cardiac output was measured with the indocyanin green dye–dilution technique using a cardiac output computer.* With these measurements, the following were calculated: cardiac index (CI) (ml/min/kg), stroke volume index (SVI) (ml/beat/kg), stroke work index (SWI) (gm-m/kg), and systemic resistance index (SRI) (dynes sec cm^{-5}/kg).

$$\text{SWI} = [(\text{mean AP} - \text{LVEDP}) \times \text{SVI} \times 1.36]/100$$
$$(\text{SRI}) = [(\text{mean AP} - \text{LVEDP}) \times 80]/\text{CI}$$

where AP = aortic pressure.

Regional myocardial function was assessed through the sonomicrometric signals. Measurement of end-diastolic (EDL) and end-systolic (ESL) lengths allowed calculation of systolic shortening (ΔL) ($\Delta L = \text{EDL} - \text{ESL}$), and percentage of systolic shortening ($\%\Delta L$) was

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*6F arterial catheter with a pressure administration cuff manufactured by Sorenson Research Co, Salt Lake City, UT.

*COR 100A, Waters Instruments Incorporated, Rochester, MN.

Table 1. Comparison of Mean Hemodynamic Values in the Two Groups Prior to Bypass

Determination	Potassium (N = 10)	Diltiazem (N = 10)	p Value
HR (beats/min)	152 ± 7	144 ± 6	NS
$\overline{AP}$ (mm Hg)	113 ± 6	127 ± 4	<0.05
LVP max (mm Hg)	124 ± 5	135 ± 4	NS
LVEDP (mm Hg)	4.3 ± 0.2	4.8 ± 0.3	NS
+ dP/dt (mm Hg/sec)	2,004 ± 191	1,825 ± 164	NS
− dP/dt (mm Hg/sec)	2,516 ± 124	2,286 ± 219	NS
CI (ml/min/kg)	109.4 ± 8.9	96.8 ± 8.8	NS
SVI (ml/beat/kg)	0.72 ± 0.05	0.67 ± 0.05	NS
SWI (gm-m/kg)	1.06 ± 0.09	1.10 ± 0.09	NS
SRI (dynes sec cm^{-5}/kg)	82.3 ± 6.0	105.3 ± 6.9	<0.01

HR = heart rate; $\overline{AP}$ = mean aortic pressure; LVP max = maximum left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; + dP/dt = maximum positive first derivative of LVP; − dP/dt = maximum negative first derivative of LVP; CI = cardiac index; SVI = stroke volume index; SWI = stroke work index; SRI = systemic resistance index; NS = not statistically significant.

Table 2. Comparison of Mean Hemodynamic Values before and after Two Hours of Ischemic Arrest

	Potassium (N = 10)			Diltiazem (N = 10)		
Determination	Before	After	p Value	Before	After	p Value
HR (beats/min)	152 ± 7	124 ± 8	<0.005	144 ± 6	129 ± 7	NS
$\overline{AP}$ (mm Hg)	113 ± 6	75 ± 5	<0.001	127 ± 4	100 ± 5	<0.005
LVP max (mm Hg)	124 ± 5	90 ± 4	<0.001	135 ± 4	114 ± 5	<0.005
LVEDP (mm Hg)	4.3 ± 0.2	5.2 ± 0.5	NS	4.8 ± 0.3	5.3 ± 0.3	NS
+ dP/dt (mm Hg/sec)	2,004 ± 191	1,585 ± 119	<0.01	1,825 ± 164	1,760 ± 151	NS
− dP/dt (mm Hg/sec)	2,516 ± 124	1,192 ± 157	<0.001	2,286 ± 219	1,648 ± 126	<0.01
CI (ml/min/kg)	109.4 ± 8.9	80.0 ± 6.9	<0.005	96.8 ± 8.8	121.7 ± 8.6	<0.005
SVI (ml/beat/kg)	0.72 ± 0.05	0.66 ± 0.07	NS	0.67 ± 0.05	0.94 ± 0.03	<0.001
SWI (gm-m/kg)	1.06 ± 0.09	0.63 ± 0.09	<0.001	1.10 ± 0.09	1.16 ± 0.05	NS
SRI (dynes sec cm^{-5}/kg)	82.3 ± 6.0	75.4 ± 9.6	NS	105.3 ± 6.9	62.2 ± 5.3	<0.001

Abbreviations same as for Table 1.

obtained by dividing ΔL by EDL and multiplying the product by 100 [30]. Instantaneous velocities were obtained through differentiation of the sonomicrometric signals (max S dL/dt or maximum systolic velocity).

AFTER CLAMPING. The same variables were measured 30 minutes after cessation of CPB or 60 minutes following unclamping of the aorta at a time when the heart was in sinus rhythm, body temperature was 37°C, and arterial pH was 7.40.

Results were analyzed with the Student paired t test, and the probability (p) was deemed significant when less than 0.05. All data were expressed as the mean value plus or minus the standard error of the mean.

Results

Before Cardiopulmonary Bypass

As shown in Table 1, the variables measured were comparable in both groups before bypass except for the higher SRI ($p < 0.01$) and mean aortic pressure ($p < 0.05$) in Group 2.

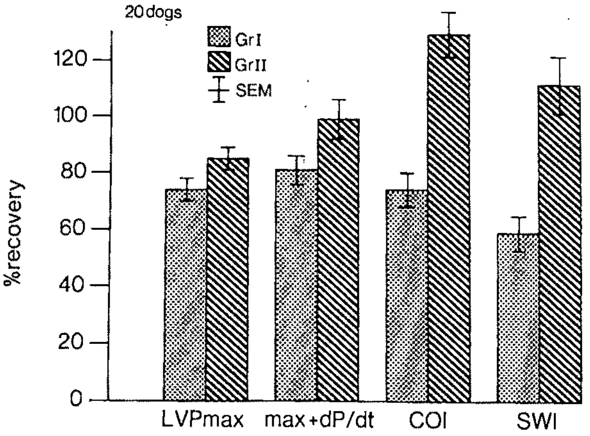
After Cardiopulmonary Bypass

Results obtained one hour after reperfusion are summarized in Tables 2 through 4 and the Figure.

Table 3. Comparison of Mean Hemodynamic Values in the Two Groups after Two Hours of Ischemic Arrest and One Hour of Reperfusion

Determination	Potassium (N = 10)	Diltiazem (N = 10)
HR (beats/min)	124 ± 8	129 ± 7
$\overline{\text{AP}}$ (mm Hg)	75 ± 5	100 ± 5
LVP max (mm Hg)	90 ± 4	114 ± 5
LVEDP (mm Hg)	5.2 ± 0.5	5.3 ± 0.3
+ dP/dt (mm Hg/sec)	1,585 ± 119	1,760 ± 151
− dP/dt (mm Hg/sec)	1,192 ± 157	1,648 ± 126
CI (ml/min/kg)	80.0 ± 6.9	121.7 ± 8.6
SVI (ml/beat/kg)	0.66 ± 0.07	0.94 ± 0.03
SWI (gm-m/kg)	0.63 ± 0.09	1.16 ± 0.05
SRI (dynes sec cm^{-5}/kg)	75.4 ± 9.6	62.2 ± 5.3

Abbreviations same as for Table 1.



Percent of recovery in maximal left ventricular pressure (LVP max), *maximum positive derivative of left ventricular pressure* (max +dP/dt), *cardiac output index* (COI), *and stroke work index* (SWI) *after two hours of ischemic arrest and one hour of reperfusion in the two groups.*

LEFT VENTRICULAR PERFORMANCE. Dogs receiving KCl (Group 1) showed deterioration of LV performance. Maximal LV pressure, maximal positive dP/dt, CI, and SWI returned to 74 ± 4%, 81 ± 5%, 74 ± 6%, and 59 ± 6%, respectively, of the preclamping values (see Figure). Conversely, animals given diltiazem showed almost complete recovery of preclamping cardiac function: maximal LV pressure, maximal positive dP/dt, CI, and SWI returning to 85 ± 4%, 99 ± 7%, 129 ± 8%, and 111 ± 10%, respectively, of the initial values. Thus, following CPB, LV performance appeared better preserved in Group 2 dogs (see Table 3).

LEFT VENTRICULAR COMPLIANCE. The LVEDP did not change in either group. On the other hand, the rate of relaxation (peak negative dP/dt) decreased significantly in both groups, perhaps less so in Group 2 dogs.

REGIONAL MYOCARDIAL FUNCTION. Measurement of regional myocardial function through sonomicrometric crystals showed no significant changes in either group (see Table 4). However, the %ΔL increased in the LAD area in Group 2 animals.

Table 4. Comparison of Mean Values of Regional Myocardial Function before and after Two Hours of Ischemic Arrest

	Potassium (N = 10)			Diltiazem (N = 10)		
Determination	Before	After	*p* Value	Before	After	*p* Value
Cx area						
ΔL (%)	11.3 ± 0.9	12.8 ± 1.7	NS	12.3 ± 1.5	13.8 ± 1.4	NS
Max S dL/dt (mm/sec)	15.3 ± 2.6	15.4 ± 1.8	NS	19.5 ± 3.2	18.5 ± 2.4	NS
LAD area						
ΔL (%)	15.7 ± 1.1	14.2 ± 1.5	NS	13.4 ± 1.6	16.8 ± 2.4	<0.05
Max S dL/dt (mm/sec)	25.7 ± 3.7	20.5 ± 4.3	NS	24.4 ± 2.9	25.6 ± 3.0	NS

Cx = circumflex artery; ΔL = percent of regional shortening; Max S dL/dt = maximum systolic velocity; LAD = left anterior descending coronary artery; NS = not statistically significant.

Comment

Results of the present study confirm the protective effect of hypothermia and pharmacological cardioplegia during ischemic cardiac arrest and point to the superiority of diltiazem, a calcium channel blocker, over KCl as a membranoplegic agent. Indeed, after two hours of ischemic clamping and hypothermia, hearts of animals treated with KCl recovered 70 to 80% of their function whereas those receiving diltiazem showed complete recovery. The appropropriate dose of anticalcic agent was arrived at through trial and error: cardiodepression often follows a high dose (350 to 500 μg per kilogram) whereas at low concentration (50 to 100 μg per kilogram) cessation of electrical activity may be incomplete or of short duration. With the current dose of diltiazem (150 μg per kilogram), cardiodepression appears minimal. Its effect, like that of other anticalcic agents [8–12], may be counteracted by administration of calcium chloride. Nevertheless, transient (15 to 30 minutes) atrioventricular dissociation or block is often observed, which reverts to sinus rhythm spontaneously or with the administration of isoproterenol or sodium chloride in conjunction with calcium [12]. In order to compare the two types of cardioplegia, however, no medication capable of altering the effect of diltiazem was administered during the experiment.

Calcium ion is essential for normal excitation-contraction coupling [8, 18]. Passage of the action potential in the sarcolemma is associated with a transient rise in cytoplasmic calcium. Calcium acts as a catalyst between the membrane electrical phenomenon (excitation) and the intracellular biochemical reactions that use adenosine triphosphate (ATP) (by activating ATPase) and lead to myocardial contraction. Intracellular influx of Ca^{++} is through the slow channels and coincides with the plateau phase of the action potential. This flux is inhibited by calcium antagonist agents [8]. A decrease in calcium flux across the membrane leads to a decrease in ATP dissociation, which, in turn, causes a drop in oxygen consumption and myocardial contractility. Blocking calcium entry into smooth muscles brings about marked vasodilatation. Hence, through a drop in oxygen consumption and marked coronary dilatation, calcium antagonists create a positive balance between supply and demand and are particularly useful in situations where myocardial ischemia is suspected. To date, these agents have been used in the treatment of angina [1, 11] and, experimentally, for the prevention of ischemic damage caused by coronary occlusion [15, 23, 28, 30] and for myocardial protection during ischemic arrest [2, 21, 22, 25].

Inhibition of calcium flux across the membrane causes complete cessation of contractile activity and thus induces cardioplegia. The latter effect of calcium antagonists has been observed with both verapamil and nifedipine, and myocardial protection provided by these agents paralleled that of cold hyperkalemic solutions [22, 25]. The ideal concentration of a cardioplegic agent is a matter of importance. At high concentration, cardioplegia is achieved at the expense of persistent standstill or atrioventricular block following reperfusion [22]. Diltiazem is a new anticalcic agent remarkably effective in the treatment of coronary spasm [1] and in preventing reperfusion injury [30]. Its negative inotropic effect on the myocardium appears less than that seen with verapamil and nifedipine. The mechanism by which it protects the myocardium during ischemic arrest is not fully understood. In all likelihood, it is the result of a combination of actions: peripheral vasodilatation, coronary vasodilatation, and cessation of calcium flux.

SYSTEMIC VASODILATATION. In the present study, diltiazem-treated animals, unlike those given KCl, showed a significant drop in peripheral vascular resistances (see Table 2). This lower afterload is responsible in part for the high cardiac output after clamping noted after CPB.

CORONARY VASODILATATION. During clamping, diltiazem-induced coronary vasodilatation may have led to a rise in the noncoronary collateral circulation, which, in turn, would have helped the myocardium rid itself of metabolic waste while receiving additional energy substrates. Often noticed in clinical situations when cold KCl cardioplegia is used, the noncoronary collateral circulation proves a nuisance at times because it washes the agent away and promotes earlier resumption of myocardial activity. Cardioplegia through calcium channel blockers may be less unstable or sensitive to minute coronary lavage. In addition, coronary vasodilatation may, at the time of reperfusion, lead to early payment of the oxygen debt.

BLOCKING OF SARCOLEMMAL CALCIUM FLUX. Diltiazem acts during both critical phases of myocardial protection, i.e., during ischemia and at reperfusion. Under anoxic conditions, membrane permeability to calcium increases [24]. Excretion of calcium from the cells through exchange of sodium is an active mechanism which requires energy in the form of ATP [18]. When this exchange is hampered through depletion of ATP, uncontrolled intracellular accumulation of Ca^{++} occurs most notably in mitochondrias and contractile proteins. Ultimately, this causes rigor bonds between the thick and thin filaments [18]. Inhibition of calcium flux not only ensures cardioplegia but allows also for the saving of energy required for calcium excretion and prevents the occurrence of myocardial contracture during ischemia.

Reestablishment of coronary flow represents a critical phase, and injury during reflow is in great part due to uncontrolled accumulation of calcium in mitochondrias [20]. Diltiazem and other anticalcic agents appear capable of decreasing the extent of mitochondrial damage during reperfusion [30]. Moreover, persistent membranoplegia during the initial phase of reperfusion may not be undesirable as it allows the cell to replenish its energy stores without wasting some of the freshly delivered substrates to a useless electromechanical activity [10].

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Experimental Evaluation of Myocardial Preservation Techniques: V. A Membrane-Stabilizing Agent, Procaine Hydrochloride

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and Akio Wakabayashi, M.D.

ABSTRACT **The protective effects of procaine hydrochloride on the anoxic heart were investigated using the papillary muscle contractility of an isolated, blood-perfused rabbit heart as an index of myocardial function. Fifty-four experiments were divided into nine groups of six experiments each, in which anoxic periods (30, 45, 60 minutes) and concentration of procaine (solution 1 or control, no procaine; solution 2, 0.03%; and solution 3, 0.3%) were the variables. The hearts arrested significantly faster with solution 3 compared with solution 2 or 1 ($p <$ 0.01). After 30 minutes of anoxia, the recovery of the contractility was 81.1 ± 4.2% with solution 1, 90.7 ± 3.4% with solution 2, and 90.6 ± 3.3% with solution 3. After 45 minutes of anoxia, the recovery was 31.8 ± 19.0% with control, 67.5 ± 15.8% with 0.03% procaine, and 58.1 ± 22.8% with 0.3% procaine. After 60 minutes of anoxia, the recovery was 2.2 ± 2.7% with control, 18.7 ± 14.1% with 0.03% procaine, and 5.0 ± 7.3% with 0.3% procaine. After each anoxic period, the best recovery occurred with those hearts arrested by solution 2. Although the difference in recovery between the procaine groups was not statistically significant, a longer time was required for the hearts arrested with solution 3 to reach full functional recovery.**

This study indicated that procaine per se has a protective effect on the anoxic hearts and that although high concentration (0.3%) of procaine arrests the heart rapidly, it delays the recovery of contractions. We recommend the use of 0.03% procaine in cardioplegic solution.

Cold cardioplegia has become the most popular method of protecting the anoxic heart during open-heart operation. However, the ingredients used in the cardioplegic solution continue to be an issue [7]. Since its introduction in 1964 by Bretschneider [5], a membrane-stablizing agent, procaine hydrochloride, has been widely used in European countries [2, 4, 6, 13, 16, 18, 19], but it has never gained popularity in the United States.

Despite numerous publications on the effectiveness of procaine in preserving anoxic hearts, most of the published experimental studies have examined the effect of procaine concomitant with other factors, such as magnesium aspartate and high osmolarity [9, 16], sodium and calcium depletion [5], potassium chloride, magnesium chloride, adenosine triphosphate (ATP), and creatine phosphate [12]. In addition, there is no agreement on the optimal concentration of procaine used in cardioplegic solution. For example, Kirsch solution contains 0.3% [18]; Bretschneider solution contains 0.2% [6]; and St. Thomas' Hospital solution contains 0.02% [4].

Therefore, the present study was undertaken to determine whether procaine per se has any protective effect on the anoxic heart and if so, to compare two different concentrations (0.3% and 0.03%).

Materials and Method

An isolated, blood-perfused rabbit heart preparation previously described [14, 21] was used. New Zealand white rabbits (average weight, 2.7 kg) were anesthetized with intravenously administered sodium pentobarbital (25 mg per

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kilogram of body weight) and ketamine hydrochloride (5 mg per kilogram). Respiration was controlled with a Harvard respirator through an endotracheal tube. The heart was rapidly excised through a midsternotomy after heparinization and immersed in cold (4°C) normal saline solution. A polyvinyl cannula (10F) was inserted into the ascending aorta as a coronary perfusion line. The left atrium was opened widely, and the mitral valve leaflets were excised to free the tip of the posterior papillary muscle. The posterior papillary muscle was then suspended between a fixed point and a force/displacement transducer (Grass FT. 03C) using fine sutures (Fig 1). The force/displacement transducer was mounted on a micrometer so that the papillary muscle could be stretched to the desired length.

The perfusion circuit consisted of a roller pump, membrane oxygenator, activated charcoal hemoperfuser [8], bubble trap/Dacron wool filter, heat exchanger, and overflow reservoir (Fig 2). The circuit was primed with 80 ml of autologous blood and 40 ml of 5% dextrose in lactated Ringer's solution, reducing the hematocrit to approximately 20%. The myocardial temperature was kept at 37°C throughout the experiment by placing the heart in a chamber containing a helical heat exchanger. The perfusion pressure was monitored through a side arm connected to the perfusion cannula, and was maintained at a constant level (80 mm Hg).

After the initiation of coronary perfusion, the contractility of the heart was measured as follows: The posterior papillary muscle was stretched by elevating the micrometer at a speed of approximately 0.2 seconds in increments of 0.5 mm every 5 seconds. Net developed tension was calculated by substracting resting tension from total developed tension: $T_N = T_T - T_R$ where T_N is net developed tension, T_T is total developed tension, and T_R is resting tension. The papillary muscle was stretched until the maximal net developed tension (T_{Nmax}) was recorded. T_{Nmax} was measured every 15 minutes, and reached a plateau usually within one hour. The plateau value was used as the baseline T_{Nmax}. Fifty-four experiments were divided into nine groups, six experiments each, in which the anoxic periods and the concentration of procaine in the cardioplegic solution were the variables (Table 1). The cardioplegic solution was made of isotonic electrolyte solution (sodium, 135 mEq/L; potassium, 5 mEq/L; chloride, 140 mEq/L) and procaine hydrochloride. The pH of the solution was adjusted to 7.4 at 37°C with TRIS buffer. The concentration of procaine was 0 (solution 1, control), 0.03% (solution 2), or 0.3% (solution 3). After one hour of baseline perfusion, the heart was arrested by infusing 10 ml of test solution 1, 2, or 3 (37°C) into the coronary perfusion line over a period of a minute. The time required to stop contractions was defined as arrest time. After a set period of normothermic anoxia, coronary perfusion was started. Initial venous effluent was discarded to avoid contamination of the coronary perfusion blood with procaine. The time required for resumption of contraction (restarting time) was measured. T_{Nmax} was measured every 15 minutes until recovery reached a plateau. The recovery of the myocardial con-

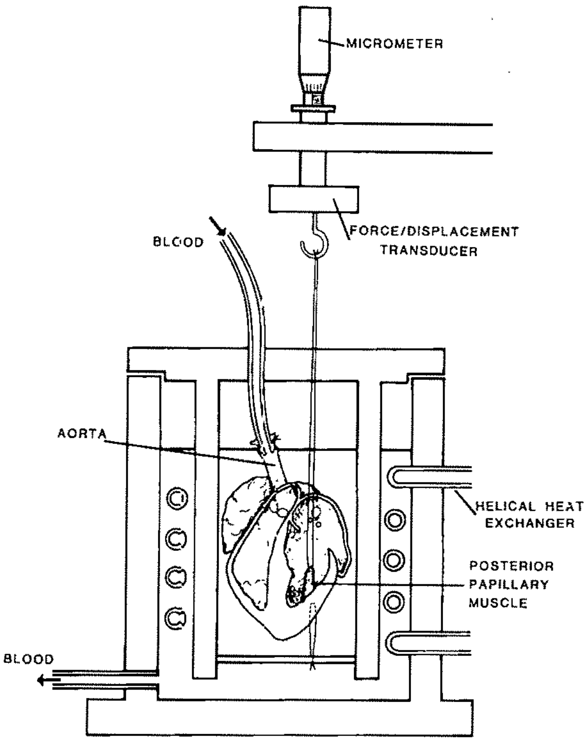

Fig 1. Diagram of rabbit papillary muscle preparation (cross section). The posterior papillary muscle is interposed between a fixed point and a force/displacement transducer, which is mounted on a micrometer.

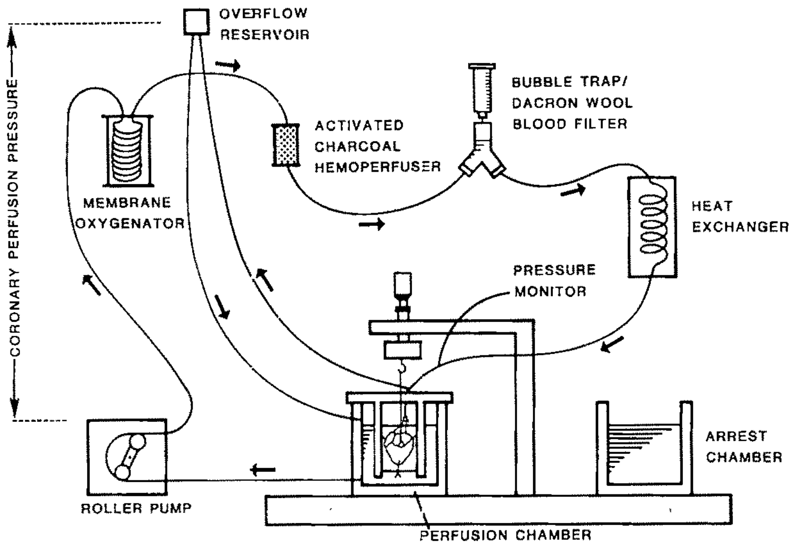

Fig 2. The perfusion circuit. The arrow indicates the direction of perfusion flow.

Table 1. Groups of Experiments

Group	No. of Experiments	Anoxic Time (min)	Solution	Procaine Hydrochloride (%)
1	6	30	1	0
2	6	30	2	0.03
3	6	30	3	0.3
4	6	45	1	0
5	6	45	2	0.03
6	6	45	3	0.3
7	6	60	1	0
8	6	60	2	0.03
9	6	60	3	0.3

tractility was expressed as a percentage of the baseline T_{Nmax}.

During the experiments, myocardial temperature, blood gases, pH, and hematocrit were measured periodically. The results of the studies were expressed as the mean ± the standard deviation of the mean and were compared by Student's t test.

Results

Surgical preparation of the papillary muscle required approximately 10 minutes of anoxia in cold saline solution. As soon as coronary perfusion with normothermic oxygenated blood was begun, all hearts started to contract spontaneously. After a brief period of arrhythmia, all hearts maintained normal sinus rhythm with rates ranging from 140 to 220 beats per minute (171 ± 21). No electrical pacing was used in this experiment. Upon resumption of coronary perfusion following cardioplegia, all hearts returned to normal sinus rhythm spontaneously. The heart rates after cardioplegia ranged from 110 to 210 beats per minute (137 ± 16), approximately 80% of the baseline.

There was a remarkable difference in arrest time among the three groups with different concentrations of procaine (Table 2). When solution 3 was used, contractions of the heart stopped very rapidly (0.6 ± 0.5 minutes; mean value of arrest time in Groups 3, 6, and 9). In contrast when solution 1 (no procaine) was used, arrest time was longer (11.7 ± 2.0 minutes; mean value of arrest time in Groups 1, 4, and 7). The arrest time with solution 2 was 7.3 ± 2.1 minutes (mean value of arrest time in Groups 2, 5, and 8), which was significantly ($p < 0.01$) shorter than that with solution 1 but significantly longer ($p < 0.01$) than that with solution 3.

The concentration of procaine also had an effect on the restarting time of the arrested hearts (see Table 2). A significantly longer restarting time was observed when the hearts were arrested with solution 3 than those arrested with solution 1 or 2. However, there was no differ-

Table 2. Arrest Time and Restarting Time

Group	Procaine Hydrochloride (%)	Arrest Time (min)	Restarting Time (min)
1	0	12.2 ± 1.5	1.3 ± 0.4
2	0.03	8.7 ± 1.0	1.1 ± 0.3
3	0.3	0.4 ± 0.2	2.6 ± 0.8
4	0	11.8 ± 2.8	1.9 ± 0.5
5	0.03	7.2 ± 2.8	2.0 ± 0.5
6	0.3	0.8 ± 0.7	2.6 ± 0.8
7	0	10.9 ± 1.5	2.6 ± 0.8
8	0.03	6.1 ± 1.6	2.1 ± 0.7
9	0.3	0.5 ± 0.3	3.2 ± 0.7

Table 3. Recovery of Maximal Net Developed Tension

Group	Procaine Hydrochloride (%)	Anoxia Period (min)	Recovery (%)
1	0	30	81.1 ± 4.2
2	0.03	30	90.7 ± 3.4
3	0.3	30	90.6 ± 3.3
4	0	45	31.8 ± 19.0
5	0.03	45	67.5 ± 15.8
6	0.3	45	58.1 ± 22.8
7	0	60	2.2 ± 2.7
8	0.03	60	18.7 ± 14.1
9	0.3	60	5.0 ± 7.3

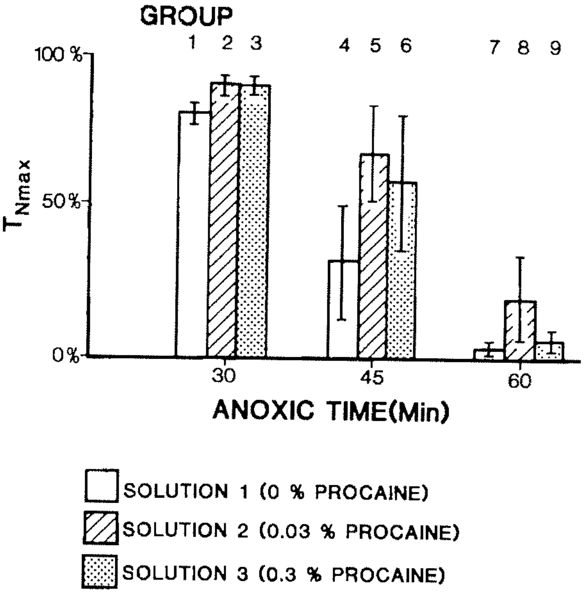

Fig 3. Recovery of contractility. The height of each bar represents the mean value of the percentage of recovery of myocardial contractility with standard deviation. (T_{Nmax} = maximal net developed tension.)

ence in restarting time among the groups in which either solution 1 or 2 was used.

The T_{Nmax} gradually recovered and reached a plateau approximately 60 minutes after coronary perfusion was started. The recovery was slower when the hearts were arrested with solution 3 than with solution 2. The final recovery rates of all nine groups are shown in Table 3 and Figure 3. After 30 minutes of anoxia, the recovery of myocardial contractility was 81.1 ± 4.2% in Group 1, 90.7 ± 3.4% in Group 2, and 90.6 ± 3.3% in Group 3. The recovery in Groups 2 and 3 receiving procaine was significantly better than in Group 1 ($p < 0.01$). There was no difference in recovery of the myocardial contractility between Groups 2 and 3. After 45 minutes of anoxia, the recovery was 31.8 ± 19.0% in Group 4, 67.5 ± 15.8% in Group 5, and 58.1 ± 22.8% in Group 6. The best recovery was observed in Group 5 (0.03% procaine). The differences between Groups 4 and 5 and Groups 4 and 6 were statistically significant ($p < 0.05$). Sixty minutes of anoxia was poorly tolerated in all groups. The recovery of Group 8 (0.03% procaine) was, however, again the best of the three groups. The difference between Groups 7 and 8 was statistically significant ($p < 0.05$) but not that between Groups 7 and 9.

Comments

Blood-perfused rabbit's papillary muscle model has been utilized in our laboratory during the last six years in the assessment of various techniques of myocardial preservation during anoxia. We found that this method is more reproducible and quantitative than left ventricular function curves of an in situ heart or Langendorff preparation.

Any cardioplegia technique to be used must protect myocardial function. Although papillary muscle tension is not directly correlated with left ventricular pressure, the myocardial contraction is the basic key element governing the left ventricular function, and there is a good correlation between the left ventricular filling pressure and myocardial sarcomere length [20]. As the sarcomere length increases, the left ventricular filling pressure rises. A correlation between resting length and total developed tension of the papillary muscle in our preparation was found to be very similar to that between left ventricular filling pressure and systolic pressure [14]. The velocity of displacement of the papillary muscle was not mechanically controlled but manual control was accurate enough to measure net developed tension, which was around 30 to 35 gm.

Bretschneider [5] described cardioplegia induced by sodium-free, procaine-containing (0.3%) solution. He demonstrated that myocardial oxygen consumption of dogs subjected to cardioplegia by his solution decreased one-fourth to one-sixth of the control using hypothermia alone. Kirsch and colleagues [18] developed a cardioplegic solution that consisted of 0.3% procaine, 2.5% magnesium aspartate (159 mEq/L), and 4.5% sorbitol (247 mM/L). The effectiveness of the Kirsch solution in rabbit and human hearts was shown by Döring and associates [9] by means of metabolic and ultrastructural studies. They also reported good clinical results with Kirsch solution [2, 16, 18].

Hearse and co-workers [12] tested various cardioplegic agents utilizing a modified Langendorff preparation. In their preliminary study, the addition of 0.2% procaine to the perfusate prior to 30 minutes of normothermic ischemia improved the recovery of aortic flow rate to 26.6% from zero recovery without procaine. When procaine concentration was reduced from 0.2% to 0.027%, the recovery of aortic flow rate decreased only slightly—from 89.2% to 82.2%. Based on these studies, they [12] developed a cardioplegic solution which is referred to as St. Thomas' Hospital solution. It contains a low concentration of procaine (0.027%) and moderately high concentration of potassium and magnesium. Jynge and colleagues [15] compared the efficacy of Bretschneider, Kirsch, and St. Thomas' Hospital cardioplegic solutions using a rat heart model. They concluded that St. Thomas' Hospital solution was effective under all conditions studied, whereas the Bretschneider solution was effective only under hypothermic conditions and the Kirsch solution was ineffective under all conditions and may increase tissue injury. They suggested the absence of calcium in the Bretschneider and Kirsch solutions might account for the myocardial damage.

In all experiments just described, other protective agents such as potassium, magnesium, creatine phosphate, ATP, or hypothermia were not separated from procaine. Thus, the beneficial effects of the method could not be solely attributed to procaine. Since procaine was the only active ingredient in our cardioplegic solution, any protective effects seen in our study should be attributed to procaine. Our data showed that the recovery of myocardial contractility after 30 minutes of normothermic anoxia was significantly improved by procaine. When anoxic periods were extended to 45 and 60 minutes, 0.03% procaine continued to show protective effects on the anoxic hearts but to a lesser degree.

Bixler and colleagues [1] compared procaine cardioplegia (0.2%) and potassium cardioplegia (37 mEq/L) by measuring carbon dioxide tension of the anoxic myocardium of an isolated cat heart. They demonstrated that at normothermia procaine cardioplegia produced a significantly lower carbon dioxide tension than control but failed to preserve ventricular function and to prevent myocardial edema. When used at 27°C, both procaine and potassium cardioplegia were able to restore ventricular function after arrest better than the controls. Less myocardial edema formation was noted in the potassium-arrested hearts than the others. They concluded that potassium cardioplegia was superior to procaine cardioplegia. In our previous study [21], we demonstrated that the functional recovery of the hearts arrested by potassium chloride (40 mEq/L) was 90.0% after 30 minutes of normothermic anoxia. We did not study water content of the myocardium, but this functional recovery rate was quite similar to those of the procaine-arrested hearts in the present study (90.7% with 0.03% procaine and 90.6% with 0.3% procaine). We believe that procaine cardioplegia is as effective as potassium cardioplegia at normothermia. The reason for the difference between our results and those of Bixler and associates [1] under normothermic conditions may be due to different animal species and a different experimental model. It should be noted, however, that in their experiments the procaine group was arrested with Bretschneider solution, whereas the control group was injected with Krebs-Ringer's-bicarbonate dextran solution.

The mechanism of action by which procaine protects the anoxic heart is not completely understood. It is said that procaine stops the excitation process of the membrane by preventing the Na^+-Ca^{++} permeation [5, 16], reduces the metabolism during arrest by inhibiting membrane ATPases [9], and diminishes arrhythmias after arrest [10–12]. Fey and colleagues [10] studied the effects of membrane-stabilizing agents, procaine, and steroids, using a dog cardiopulmonary bypass model. They demonstrated that membrane stabilization with steroids, procaine, or both significantly reduced the functional depression following one hour of ischemic arrest with topical hypothermia at 14°C. Postischemic left ventricular performance returned to 97% with 0.2% procaine, compared with 55% with hypothermia alone. Procaine-treated hearts came to complete electromechanical arrest within 2 minutes after the administration of procaine. The hearts started to beat spontaneously after release of the aortic clamp and did not require defibrillation. However, procaine and steroids did not prevent edema formation after ischemia. They explained that procaine caused edema because it inhibited sodium efflux from the myocardial cell.

Despite rapid cardiac arrest, 0.3% procaine did not improve the recovery of the myocardial contractility any better than 0.03% procaine did. It is possible that the myocardial depressant effect of procaine [3] persisted long after the hearts were reperfused and started to beat. Although the actual difference in restarting time among the three tested solution groups was very small, a longer time was required for the heart to fully recover when 0.3% procaine was used than 0.03% procaine. Buckberg [7] warned that the effects of procaine cardioplegia on the myocardial cell persist, despite its washout by noncoronary collateral flow. Buckberg's group observed in patients that the resumption of cardiac contraction delayed for 20 to 30 minutes after coronary reperfusion when multidose procaine (0.2%) cardioplegia was employed.

The effectiveness of procaine cardioplegia appears nearly equal to that of potassium cardioplegia, as mentioned earlier. Both procaine and potassium induce rapid cardiac arrest. However, the mechanisms of action of these two agents are different [2, 9]. Therefore, it may be reasonable to assume that the combination of procaine and potassium might offer the more effective myocardial protection. This hypothesis was supported by Kay and associates [17], who demonstrated the additive effect of procaine to hypothermic potassium cardioplegia using a dog cardiopulmonary bypass model.

After this study, we reached two conclusions. (1) Procaine per se has a protective effect on the anoxic heart. (2) Low concentration of procaine (0.03%) such as used in the St. Thomas' Hospital solution provides better myocardial protection than high concentration of procaine used in the Kirsch or Bretschneider solution.

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Determination of Maximal Ischemic Tolerance of the Human Heart by Ultrastructural Recording of Preischemic Degree of Myocardial Hypertrophy and Degeneration

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ABSTRACT **Three biopsies were taken transmurally in different time intervals (before and after ischemia and during the reperfusion phase) from 20 patients undergoing open-heart operation for acquired valvular heart disease, and the myocardial cylinders were examined with the electron microscope. They were scrutinized to see if there is a relationship between the degree of hypertrophy and degeneration before ischemia and the extent of ischemic damage after a certain ischemia period, and between the damage before ischemia and the postoperative outcome of the patients.**

Our results show that the ischemic changes are not dependent on the preischemic extent of hypertrophy and degeneration. It seems that they are mainly dependent on the duration of ischemia because the degree of ischemic damage increases with prolongation of the ischemia interval. However, a good correlation was found between the preischemic changes and the postoperative outcome. Especially the combination of marked hypertrophy and the appearance of degenerative signs in the biopsy taken before ischemia seems to predestine a bad postoperative course. Therefore, it can be concluded that the total damage to the myocardial cells, which results from the sum of previous damage (hypertrophy and degeneration) and ischemic alterations, is responsible for the postoperative outcome.

For the successful performance of cardiac operations, it is important to know the ischemic tolerance of myocardial tissue. It is therefore not surprising to find in the literature many references to the maximally tolerable period of ischemia in the animal and human heart [3, 13, 15, 22, 28]. However, the results in these studies differ. Some of the differences can be explained by variations in operative technique, myocardial protection, and sample removal, but the differences in these variables cannot be used to explain such divergent results. Therefore, it is possible that the initial condition of the myocardium (the degree of hypertrophy and degeneration visible on electron microscopic study) may influence the ischemic tolerance.

The purpose of this study was to investigate the influence of the preischemic extent of myocardial cell hypertrophy and degeneration on the extent of ischemic damage and on the postoperative outcome.

Material and Methods

Cardiac biopsy specimens were taken from 20 patients undergoing open-heart operation for acquired valvular heart disease. Clinical data on the patients are shown in Table 1. The operations were performed in a state of mild hypothermia (blood temperature, 32° to 33°C). Cardiac arrest was induced by injection of a perfusion cardioplegic solution developed at our clinic.

The biopsies for electron microscopy were removed transmurally from the left ventricular apical region using a Tru-Cut steel puncture needle from Travenol Laboratories, Inc. The first biopsy was always obtained immediately prior to aortic occlusion, the second shortly before the aortic clamp was opened, and the third after a certain time allowed for reperfusion. The myocardial cylinders were then immediately fixed in a buffered solution of 2.5% glutaraldehyde for two to six hours. They were further routinely processed, embedded in Vestopal W, and viewed in an Elmiscop 101 (Siemens).

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Table 1. Clinical Data

Patient, Age (yr), Sex	Diagnosis	Time (min)	
		Ischemia	Reperfusion until Biopsy
1. 56, F	Combined aortic-mitral disease	62	11
2. 57, F	Aortic insufficiency; combined mitral disease; stenosis of left anterior descending coronary artery	55	10
3. 47, M	Aortic stenosis	56	13
4. 52, M	Mitral insufficiency	66	15
5. 45, M	Aortic stenosis	71	12
6. 75, F	Aortic stenosis	40	7
7. 49, M	Combined aortic-mitral disease	68	11
8. 28, F	Aortic insufficiency	50	. . .
9. 50, M	Severe aortic and moderate mitral insufficiency	39	11
10. 49, F	Combined aortic disease; mitral insufficiency	61	6
11. 52, F	Aortic stenosis	68	10
12. 37, M	Combined aortic disease	57	11
13. 58, M	Aortic stenosis	50	11
14. 57, F	Aortic insufficiency	51	10
15. 68, F	Combined aortic disease	45	7
16. 56, F	Aortic stenosis	62	7
17. 50, M	Combined aortic disease; stenosis of right coronary artery	63	6
18. 58, M	Combined aortic disease	63	. . .
19. 49, M	Combined aortic disease	64	. . .
20. 53, M	Combined aortic disease	63	. . .

It is well known that the degree of myocardial cell damage visible on electron microscopic study differs from one cell to another, although the biopsies always originate from the left ventricular apical region [1, 2, 9, 28]. Therefore, we prepared four to six specimens from material obtained in each biopsy. The results described in this paper represent the average values found in these four to six specimens of each biopsy examined with the electron microscope.

Results

All biopsies taken prior to the ischemia periods were examined as to the degree of hypertrophy and degeneration. Therefore, all known signs of cellular and subcellular hypertrophy and degeneration [4, 6–12, 14, 16–21, 23–26, 29] that were recognized at least twice in four samples were noted. The biopsies taken shortly before the aortic clamp was opened and those taken after a certain time of reperfusion were examined for the degree of ischemia, on the basis of the known ultrastructural signs of ischemia [27]. Using these ultrastructural criteria, a certain number of signs of hypertrophy, degeneration, or ischemia were found in each biopsy from the 20 patients (Table 2; Figs 1–4).

To answer the question if there is a relationship between the degree of hypertrophy and degeneration before ischemia and the extent of ischemic damage, we divided the ischemia period into four intervals because the absolute ischemia phase is exceedingly important. These intervals were as follows: up to 40 minutes; from 41 to 50 minutes; from 51 to 60 minutes; and from 61 to 71 minutes.

Each visible sign of hypertrophy and each sign of ischemia was rated one point, and signs of degeneration were awarded three points

Table 2. Ultrastructural Findings before and after Ischemia and in the Reperfusion Phase

Patient No.	No. of Signs Preoperatively	Ischemia Signs before Aortic Clamp Opened	Ischemia Signs in Reperfusion Phase
1	6 (h)	3	3
2	3 (h) 1 (d)	7	7
3	7 (h)	5	2
4	4 (h)	2	2
5	6 (h)	8	10
6	6 (h) 1 (d)	3	9
7	4 (h)	3	3
8	4 (h)	4	. . .
9	7 (h) 2 (d)	2	2
10	3 (h)	5	6
11	Endo 4 (h) 2 (d) Trans 6 (h) 2 (d)	7	11
12	5 (h)	4	7
13	6 (h)	4	3
14	6 (h)	2	2
15	Endo 7 (h) 3 (d) Trans 6 (h) 3 (d)	6	8
16	Endo 5 (h) 1 (d) Trans 5 (h)	10	11
17	4 (h)	4	2
18	6 (h)	3	. . .
19	3 (h)	7	. . .
20	4 (h)	2	. . .

h = hypertrophy; d = degeneration; Endo = endocardial biopsy specimen; Trans = transmural biopsy specimen.

each. Then, the ischemia signs were placed on the abscissa and the previous damage on the ordinate of a graph. As the Figures 5 through 8 show, there is no relationship between the preischemic and ischemic damage. For Figure 8, we calculated a correlation coefficient of $r = 0.1742$ ($p > 0.05$), which confirmed this result.

To examine the possibility of a connection between the preischemic cell damage and the postoperative outcome, we noted the clinical complications three to twelve months postoperatively and compared them with the degree of hypertrophy and degeneration before ischemia. We divided the clinical myocardial complications into three groups: no complications; mild to severe complications (tachyarrhythmia to cardiac shock); and death.

Figure 9 shows a significant correlation ($r = 0.5899$; $p < 0.01$) between the signs of hypertrophy and degeneration and the myocardial complications. Thereby it is obvious that patients whose myocardium showed up to seven signs of hypertrophy (and no degeneration) had a postoperative outcome free from complications. However, the postoperative complications increase with any additional increase in hypertrophy or with beginning degeneration. For example, Patient 15 with six signs of hypertrophy and three signs of degeneration died of heart failure on the seventh postoperative day.

Comment

As Figures 5 through 8 emphasize, the ischemic changes are not dependent on the degree of myocardial cell hypertrophy or degeneration. The same result is found when only the signs of hypertrophy and ischemia are compared. This means that a severely hypertrophied and degenerated cell does not necessarily show many marked ultrastructurally visible alterations after ischemia. Examples of this are Patients 3, 6, 9, and 14. On the other hand, relatively mildly hypertrophied cells can be severely damaged by ischemia, as in Patients 10 and 19.

Our results show that the extent of ultrastructurally evident ischemic damage is dependent mainly on the duration of aortic occlusion. Hypertrophy or degeneration does not essentially alter the reactive form of the cell during ischemia. The exact biomolecular mechanisms leading to the same ischemic changes in slightly as well as severely previously damaged myocardial tissue after a certain period of aortic occlusion remain unknown.

A positive correlation was found between the extent of hypertrophy and degeneration of the

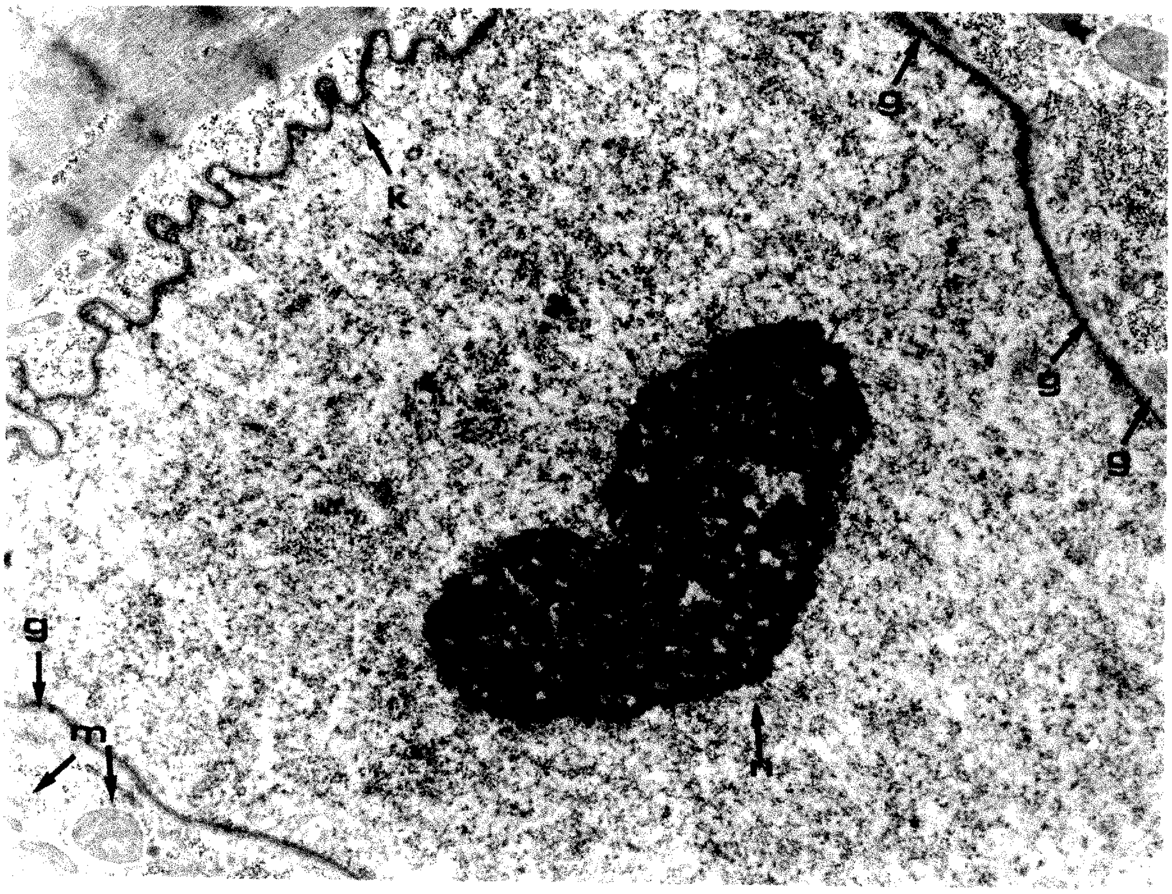

Fig 1. Electron micrograph showing a quantitative, perinuclear increase of the Golgi apparatus (g), *a folding of the nuclear membrane* (k), *a prominent nucleolus* (n), *and variability of the mitochondrial size* (m). *This corresponds with the hypertrophy signs in Table 2. (×12,000 before 5% reduction.)*

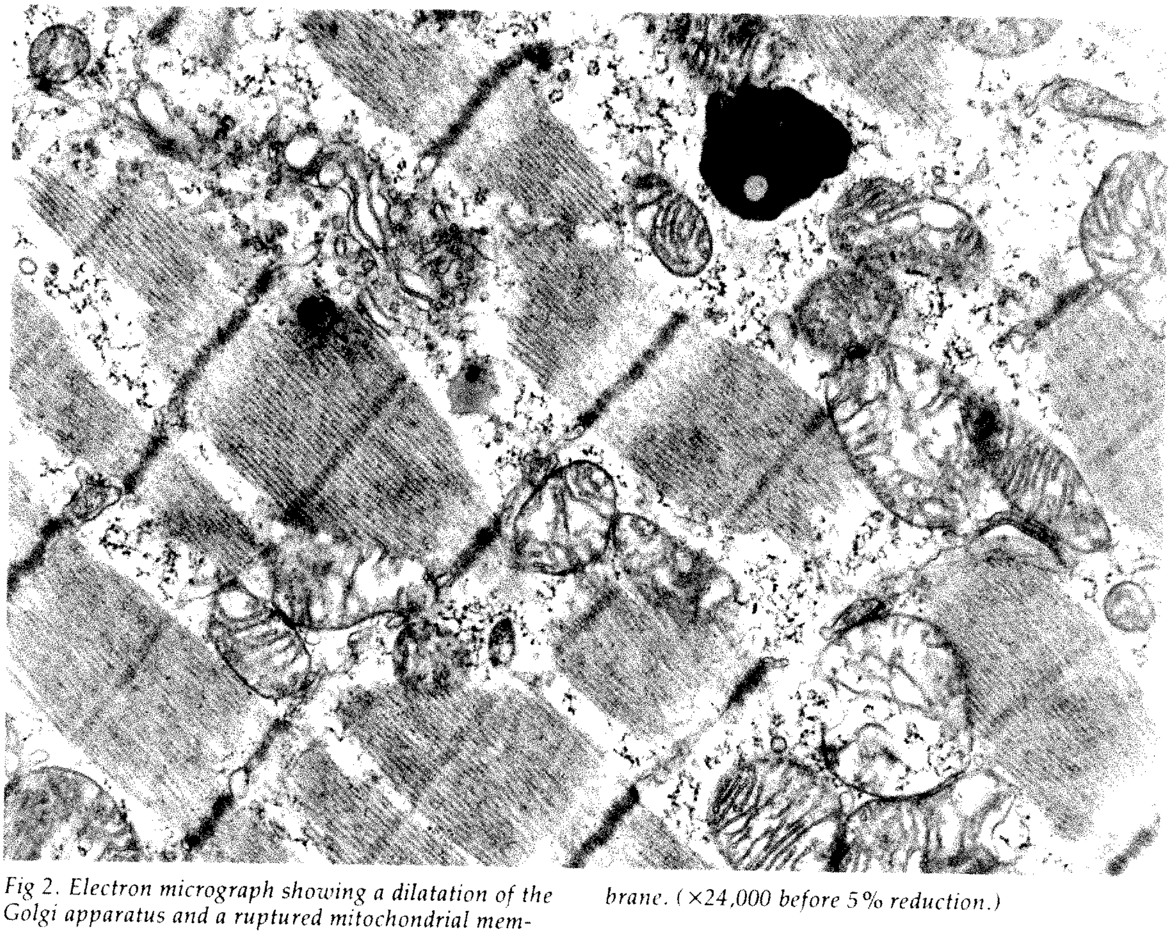

Fig 2. Electron micrograph showing a dilatation of the Golgi apparatus and a ruptured mitochondrial membrane. (×24,000 before 5% reduction.)

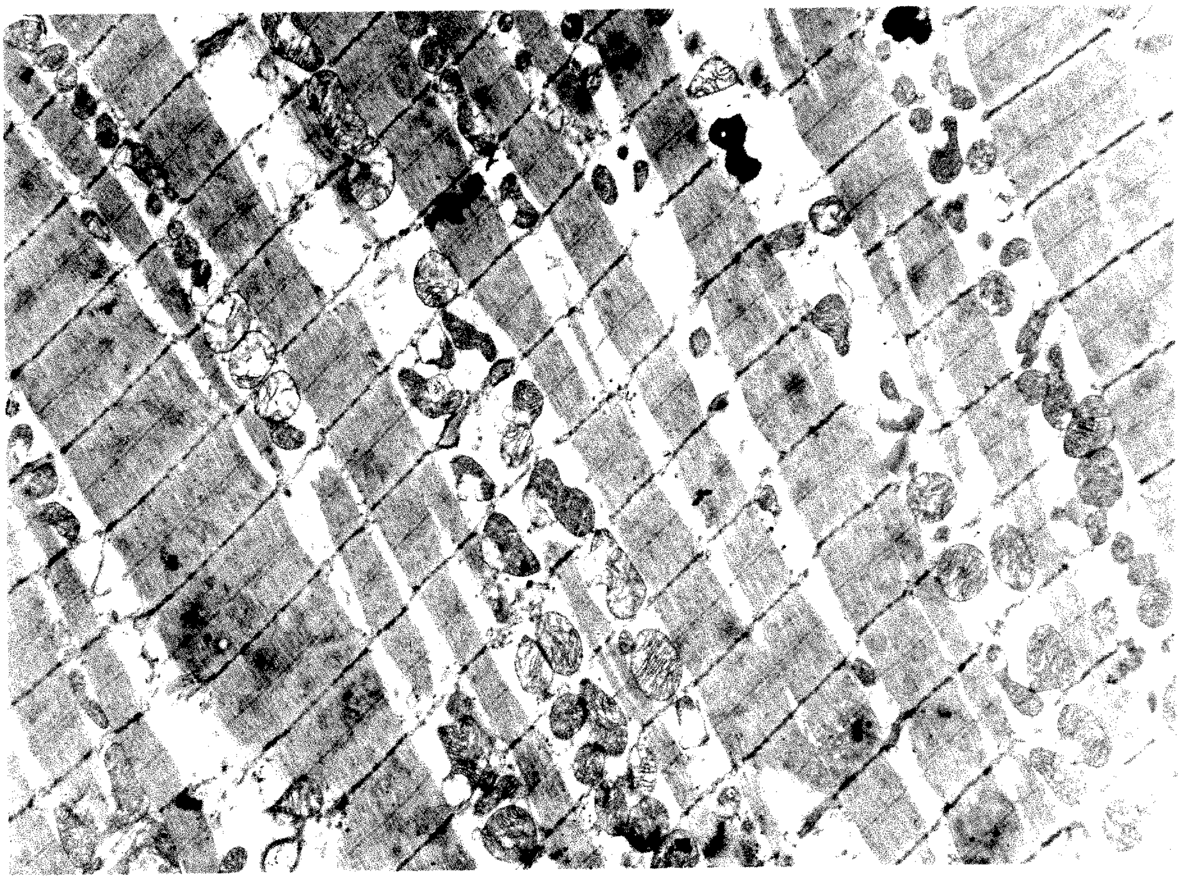

Fig 3. Electron micrograph revealing second-degree intracellular edema. (×8,000 before 5% reduction.)

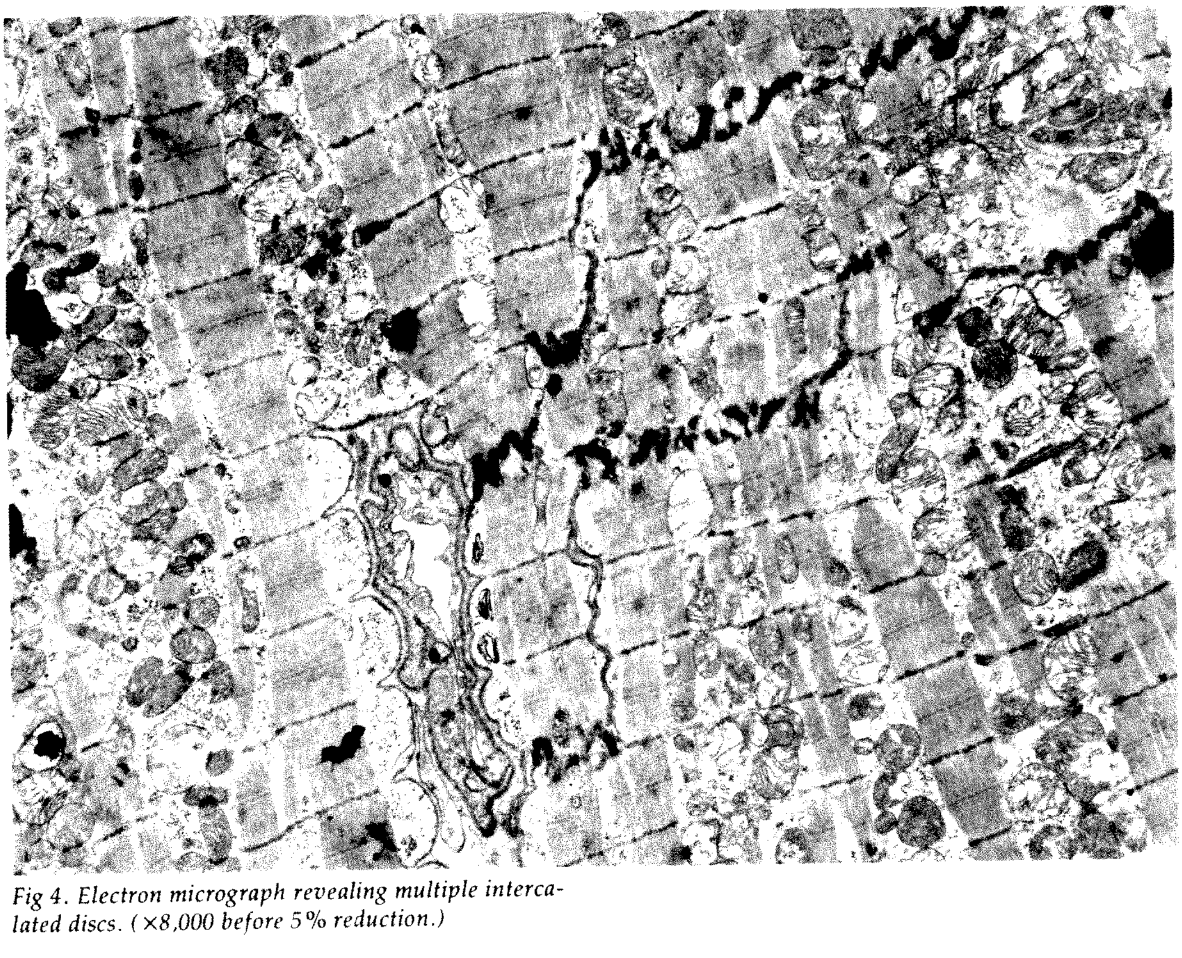

Fig 4. Electron micrograph revealing multiple intercalated discs. (×8,000 before 5% reduction.)

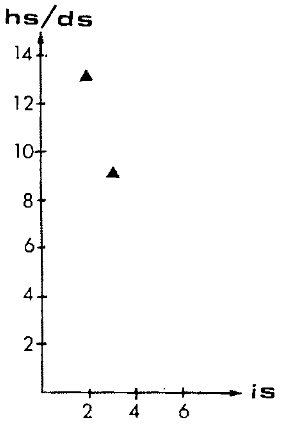

Fig 5. Up to 40 minutes of ischemia. (hs/ds = *hypertrophy/degeneration;* is = *ischemia.)*

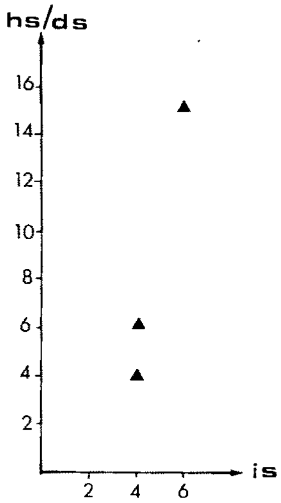

Fig 6. From 41 to 50 minutes of ischemia. (hs/ds = *hypertrophy/degeneration;* is = *ischemia.)*

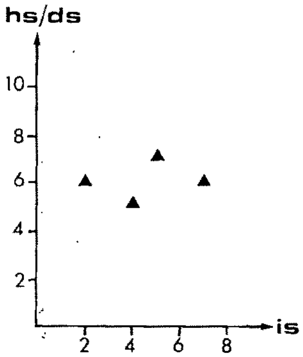

Fig 7. From 51 to 60 minutes of ischemia. (hs/ds = *hypertrophy/degeneration;* is = *ischemia.)*

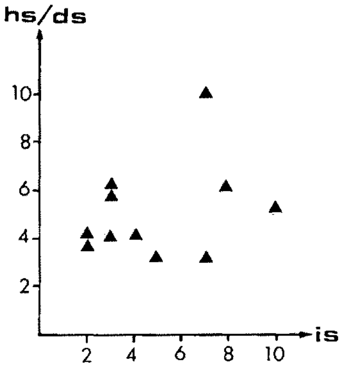

Fig 8. From 61 to 71 minutes of ischemia. (hs/ds = *hypertrophy/degeneration;* is = *ischemia.)*

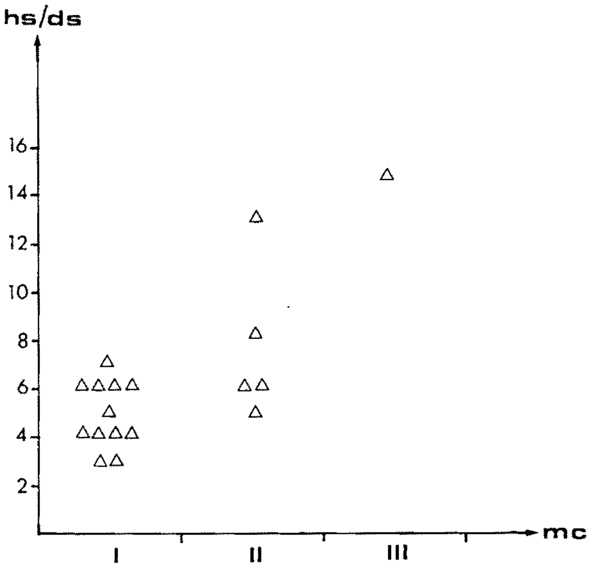

Fig 9. Correlation between the myocardial complications (mc) *and the extent of preischemic damage, i.e., hypertrophy* (hs) *and degeneration* (ds). (I = *no complications;* II = *mild to severe complications;* III = *death.)*

myocardial cell and the postoperative outcome. Our results indicate that the postoperative prognosis decreases with any marked increase in hypertrophy and especially with any increase in degeneration (see Fig 9). That means that the postoperative course is not affected only by the absolute interval of ischemia. For example, the longest interval—71 minutes—was well tolerated (Patient 5); the shortest period—39 minutes—led postoperatively to myocardial insufficiency (Patient 9).

Our results show that the postoperative outcome can also be influenced by the degree of hypertrophy and degeneration before ischemia.

This implies that the total damage to the myocardial cell is responsible for the postoperative outcome. The total damage is the sum of previous damages (hypertrophy and degeneration) and the ischemic alterations. A severely damaged myocardial tissue can lead to a poor prognosis when only slight additional impairment during ischemia occurs. On the other hand, a slightly damaged myocardium can tolerate longer periods of ischemia. These dependencies result, in practice, in a correlation between the postoperative course and the degree of hypertrophy and degeneration.

Since the extent of ischemic damage to the myocardium is relatively constant (depending on the necessary period of aortic occlusion), the degree of previous damage must be ascertained in order to determine what ischemic damages can be added without resulting in lethal impairment of the myocardium. Therefore, it is important to define the degree of myocardial damage during a time when the cardiac muscle is still able to tolerate the ischemic damages during open-heart operation.

Since cardiac catheterization was performed on all our patients before operation, it was possible to obtain an endocardial biopsy from the left ventricle in 3 patients. To explain whether the endocardial biopsy is as suitable as a transmural biopsy in determining the degree of myocardial damage, the endocardial tissue was evaluated in the same way as the transmurally obtained tissue. The morphological results of both biopsy types are seen in Table 2.

There appears to be no essential difference in the extent of damage between the endocardial and transmural biopsy specimens. Therefore, an endocardial biopsy can be considered appropriate for determining the extent of myocardial damage prior to ischemia. These results are supported by experiments performed by other authors on the differences in the epicardial, myocardial, and endocardial layers of the cardiac wall during ischemia [5, 27]. They could show that all myocardial layers are damaged to the same extent. However, a larger number of experiments is necessary to support these morphological results.

We proceeded from the assumption that deaths following open-heart operation, most of which are due to myocardial failure [30, 31], originate because already damaged myocardium is additionally damaged during operation-induced ischemia. Postoperative resumption of circulatory work is made impossible. This means that if the operation is performed during an early phase of myocardial hypertrophy, additional cardiac ischemia is well tolerated and only a few complications can be expected. However, if the operation is performed during insufficiency or end-phase hypertrophy, the additional cardiac ischemia leads to a poor prognosis. An extremely bad postoperative outcome results when one or more signs of degeneration are present in the myocardial tissue. Furthermore, it seems that study of the endocardial biopsy specimen taken during cardiac catheterization gives a chance to determine preoperatively the time (absence of degenerative signs in the myocardium) in which successful operation would still be possible.

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A Comparison of Serum Isoenzyme Levels of Creatine Phosphokinase and Lactic Dehydrogenase in Patients Undergoing Thoracic Operations and Patients Admitted to a Coronary Care Unit

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ABSTRACT **A prospective study comparing patients undergoing major thoracic surgical procedures with patients admitted to a coronary care unit was conducted. Surgical patients having bronchoscopy and mediastinoscopy (n = 12), anterior thoracotomy (n = 12), and posterolateral thoracotomy (n = 22) were compared with patients in the coronary care unit who had electrocardiographically proved myocardial infarctions (MI) (n = 11) and those with no electrocardiographic abnormalities (n = 12).**

Sera were studied by spectrophotometric analysis (creatine phosphokinase [CPK] and lactic dehydrogenase [LDH]), agarose gel electrophoresis (CPK and LDH), and antibody inhibition spectrophotometric analysis (CPK). The levels of total CPK did not rise above the upper limits of normal (100 IU/L) in patients who underwent bronchoscopy and mediastinoscopy. Total CPK elevations in patients undergoing thoracotomy (anterior thoracotomy, 428 ± 62 IU/L [mean ± standard error of the mean]; posterolateral thoracotomy, 652 ± 78 IU/L) were not significantly different from those sustaining acute MIs (463 ± 84 IU/L). Only transient minimal elevations of CPK-MB isoenzyme were noted, however, in the patients having posterolateral thoracotomy (25 ± 7 IU/L). These were significantly lower ($p < 0.001$) than the elevations seen in patients sustaining acute MIs (80 ± 16 IU/L). In none of the surgical patients did LDH_1 exceed LDH_2 while all of the patients with MIs had such a shift ($p < 0.001$). The data support the conclusion that the serum isoenzymes of CPK and LDH are capable of confirming the diagnosis of MI in patients recovering from major thoracic surgical procedures.

Confirmation of acute myocardial infarction (MI) by elevation of serum creatine phosphokinase (CPK) and lactic dehydrogenase (LDH) depends on careful determination of total activity of each enzyme and precise monitoring of temporal changes in their respective isoenzyme patterns. Elevations of total serum CPK activity are apparent within 12 to 24 hours after infarction [3]. During this time the CPK-MB band becomes prominent on serum electrophoresis and CPK-MB isoenzyme activity becomes greater than 5% of the total CPK activity [3, 4]. Serum levels of total CPK return to normal approximately five days after the infarction, whereas CPK-MB bands disappear approximately two days sooner [3]. Total serum LDH activity exceeds normal limits from 12 to 24 hours after MI, peaks at three days, and returns to normal limits within ten days after the acute episode [3]. By 48 hours after acute MI, 80% of patients will have a "flipped LDH" pattern in their serum [3]. This pattern is caused by a reversal in the normal serum pattern of the isoenzymes of LDH in which LDH_2 is the predominant isoenzyme. After MI, the levels of LDH_1 rise precipitously. LDH_1 becomes the predominant isoenzyme in the patient's serum, and the ratio of LDH_1 to LDH_2, which is normally less than 1, becomes greater than unity.

The validity of these concepts has been called into question by recent information. Regen-

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Data for the Five Patient Groups

Variable	Bronchoscopy + Mediastinoscopy	Anterior Thoracotomy	Posterolateral Thoracotomy	Coronary Care Unit Non-MI	Coronary Care Unit MI
No. of patients	12	12	22	12	11
Mean age (yr)	55.8	41.2	46.4	57.8	63.2
Age range (yr)	44–73	24–65	25–62	32–78	46–87
M:F ratio	10:2	7:5	16:6	9:3	9:2

Non-MI = no evidence of acute myocardial infarction; MI = acute myocardial infarction.

erating muscle fibers associated with specific neuromuscular diseases or trauma can cause elevation of serum CPK-MB [11]. At least five published papers report detectable levels of CPK-MB in skeletal muscle [5, 6, 8, 12, 13]. Transient elevations of CPK-MB have been noted in the sera of patients who sustained chest trauma but had no evidence of myocardial damage [7]. Because of these reports, a prospective study was conducted to determine if the isoenzymes of CPK and LDH could be used to differentiate patients who had acute MIs from patients who had recently undergone major thoracic surgical procedures.

Methods

Patients undergoing bronchoscopy and mediastinoscopy under general anesthesia (n = 12), anterior thoracotomy (n = 12), and posterolateral thoracotomy (n = 23) were included as the three groups of surgical patients. No patient undergoing combined procedures was considered. Preoperative serum samples confirmed that the isoenzymes of CPK and LDH were normal in all of the patients. Serum samples were obtained in the recovery room and daily for seven days after operation. One patient who had an intraoperative MI was eliminated from the group having posterolateral thoracotomy and is considered separately (reducing n to 22).

During the five months in which the serum samples were being obtained from surgical patients, a simultaneous evaluation of patients admitted to the coronary care unit was conducted. Those patients admitted with a diagnosis of acute MI had serum isoenzyme analyses daily for three days after admission. Patients with definite electrocardiographic evidence of MI (n = 11) were selected to be compared with the surgical patients. Patients who were admitted to the coronary care unit for possible MI based on clinical assessment but who had no MI on electrocardiogram were included as the final group (n = 12). The Table summarizes the characteristics of the five groups studied.

All blood samples were centrifuged at 3,000 revolutions per minute for ten minutes within an hour after collection. The serum was decanted and spectrophotometrically analyzed for total CPK and LDH by means of a Centrifichem series 400 autoanalyzer.* The isoenzymes of both CPK and LDH were determined using the Corning ACI agarose gel electrophoresis system equipped with a 720 densitometer and a 722 data terminal. Total serum CPK and CPK-MB were confirmed on each sample by using the Dade† Cardiozyme antibody inhibition technique in conjunction with spectrophotometric analysis (Stasar III‡ spectrophotometer with system 102 data terminal). Each determination was calibrated for accuracy against standardized controls before a series of samples was run.

The Wilcoxon rank sum test [2] was used for testing whether the distributions of a given variable (e.g., CPK-total) were the same in two comparison groups (e.g., combined anterior and posterolateral thoracotomies versus acute MIs). Observed significance levels (*p* values) were obtained using the normal approximation and are reported as one-sided values.

*Union Carbide, Rye, NY.

†Dade Division, American Hospital Supply Corp, Miami, FL.

‡Gilford Instrument Laboratories, Inc, Oberlin, OH.

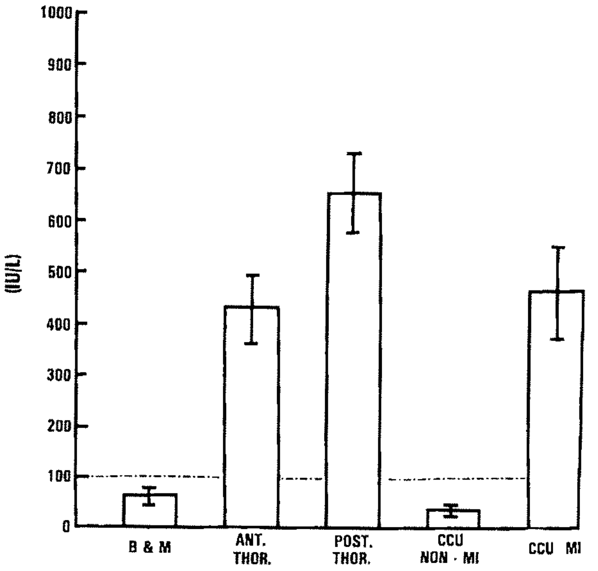

Fig 1. Maximal elevations of total serum CPK. Bars represent standard error of the mean. Interrupted line at 100 IU/L represents the upper limits of normal as established in this laboratory. (B & M = *bronchoscopy and mediastinoscopy;* ant. thor. = *anterior thoracotomy;* POST. THOR. = *posterolateral thoracotomy;* CCU NON-MI = *coronary care unit without myocardial infarction on electrocardiogram;* CCU MI = *coronary care unit with myocardial infarction.)*

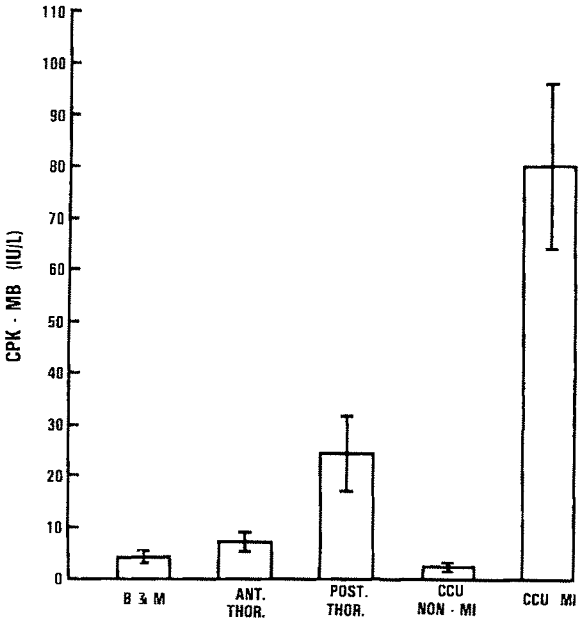

Fig 2. Maximal elevations of serum CPK-MB. Normal values for this laboratory are less than 6 IU/L. (Abbreviations same as for Figure 1.)

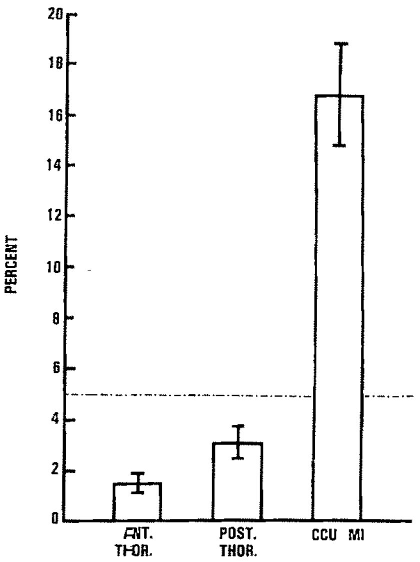

Fig 3. Percentage of total CPK, which is CPK-MB. The interrupted line at 5% represents an arbitrary dividing line between patients sustaining myocardial damage and those patients who have elevations of CPK-MB due to other causes See Results for details. (Abbreviations same as for Figure 1.)

Results

Total serum CPK was elevated above normal limits (100 IU/L) in three of the five groups studied (Fig 1). Patients who had a thoracotomy had mean maximal elevations of total CPK (anterior thoracotomy, 428 ± 62 IU/L [mean ± standard error of the mean]; posterolateral thoracotomy, 652 ± 78 IU/L) that were not significantly different from the mean maximal elevations seen in the serum of patients sustaining acute MIs (463 ± 84 IU/L). Patients who had bronchoscopy and mediastinoscopy did not have elevations of total serum CPK above the upper limits of normal.

Patients undergoing anterior thoracotomy or posterolateral thoracotomy had minimally elevated serum CPK-MB fractions (7 ± 2 IU/L and 25 ± 7 IU/L, respectively) but they were significantly less ($p < 0.001$) than the elevations found in the sera of patients with acute MI (80 ± 16 IU/L). The upper limits of normal for serum CPK-MB established in our laboratory is 6 IU/L (Fig 2). When the elevations of serum CPK-MB are expressed as a percent of the total CPK, the significant difference ($p < 0.001$) remains between the patients having a thoracotomy and the patients with an acute MI (anterior thoracotomy, 1.5 ± 0.4%; posterolateral thoracotomy, 3.1 ± 0.6%; MI, 16.9 ± 2.0%) (Fig 3).

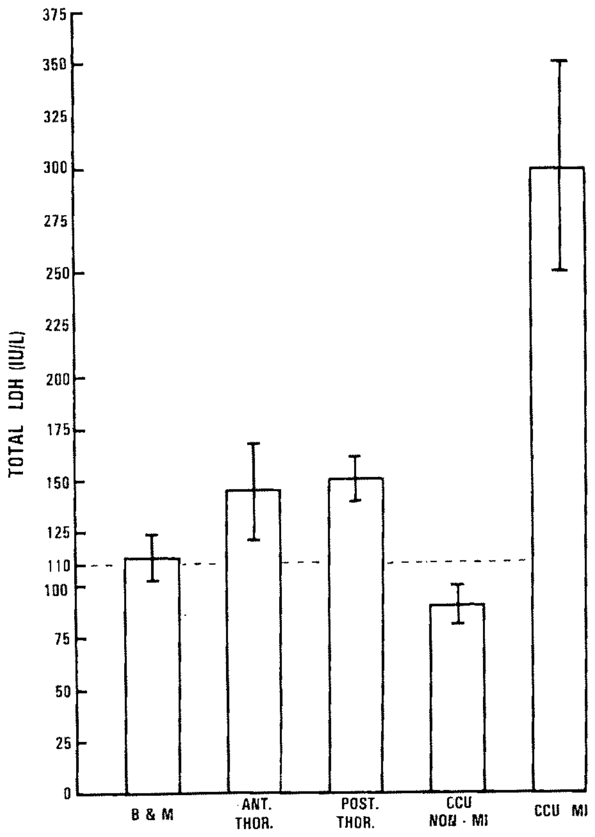

Fig 4. Maximal elevations of total serum LDH. Interrupted line at 110 IU/L represents upper limits of normal as established in this laboratory. (Abbreviations same as for Figure 1.)

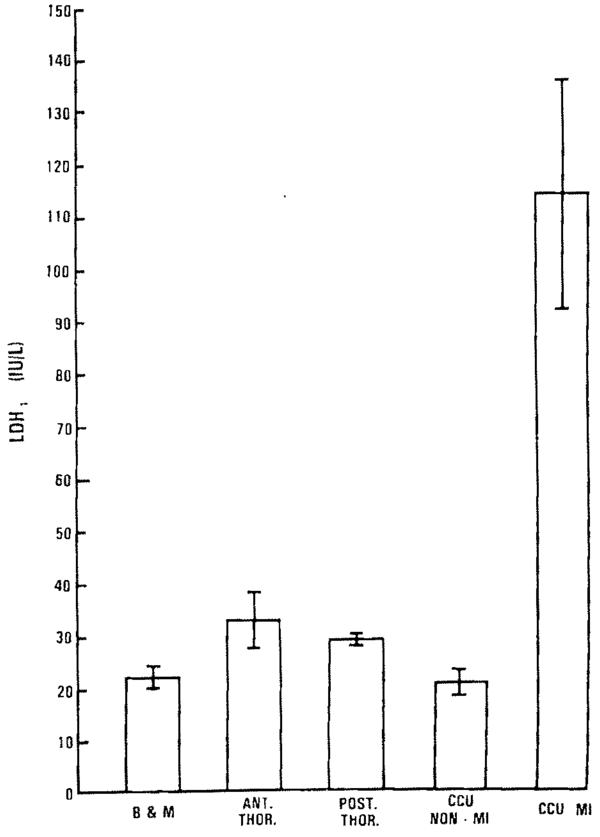

Fig 5. Maximal elevations of LDH$_1$, the predominant isoenzyme of LDH in cardiac muscle. (Abbreviations same as for Figure 1.)

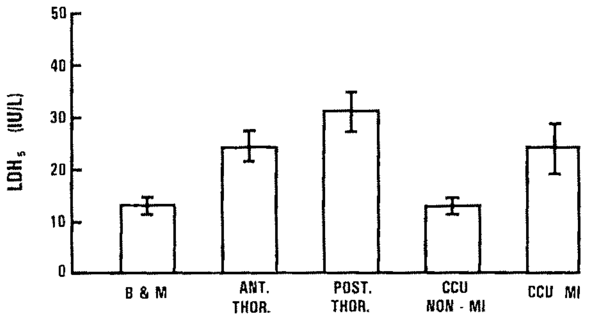

Fig 6. Maximal elevations of LDH$_5$, the predominant isoenzyme of LDH in skeletal muscle. (Abbreviations same as for Figure 1.)

Elevations of total serum LDH were greatest in patients having acute MIs (299 ± 54 IU/L). The difference between the maximal serum values recorded for the patients having an anterior thoracotomy (147 ± 22 IU/L) and those having a posterolateral thoracotomy (151 ± 11 IU/L) was significant ($p < 0.001$) (Fig 4). The principal isoenzyme component of the elevation was LDH$_1$, the predominant isoenzyme of LDH in cardiac muscle. The difference in the maximal elevations of LDH$_1$ recorded in patients having acute MIs (114 ± 22 IU/L) was significantly greater ($p < 0.001$) than in patients having thoracotomy (anterior thoracotomy, 34 ± 5 IU/L; posterolateral thoracotomy, 29 ± 2 IU/L) (Fig 5). No significant difference between the groups was noted when the mean elevations determined for LDH$_5$, the predominant isoenzyme of skeletal muscle, were evaluated (Fig 6).

All possible combinations of the variables that showed significant differences between patients having an acute MI and those having a thoracotomy were plotted. The combination that provided the greatest separation of the two groups was LDH$_1$ and CPK-MB% (Fig 7). Note that there is minimal overlap of the groups with respect to each of the two variables. Three pa-

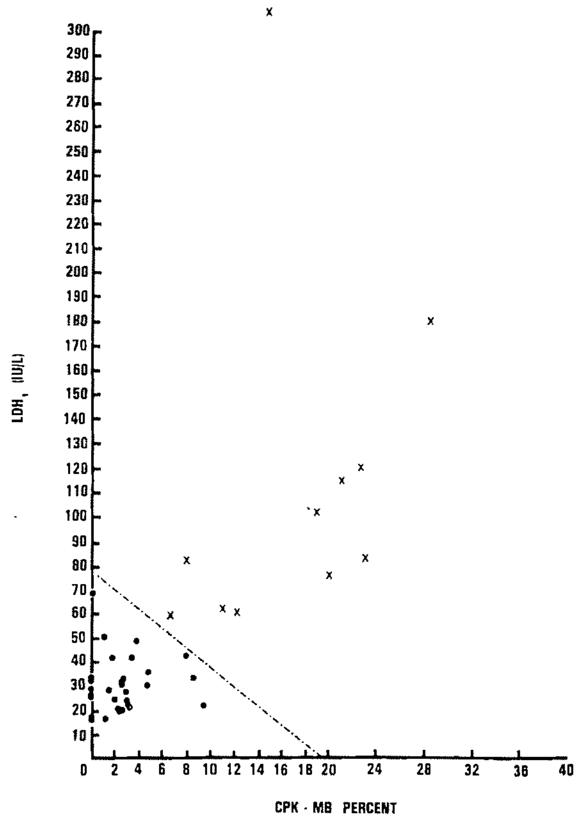

Fig 7. Composite determination of serum LDH_1 *(vertical axis) with serum CPK-MB% (horizontal axis). See Results for details. (X = myocardial infarction; • = anterior and posterolateral thoracotomy.)*

tients who had a thoracotomy had maximal elevations of CPK-MB% that exceeded 5%. One patient who had an anterior thoracotomy had a serum LDH_1 that exceeded 55 IU/L.

Comment

Several reports published previously evaluated isoenzyme changes in the sera of patients recovering from thoracic surgical procedures. Roberts and co-workers [10] could not detect any changes by electrophoresis in CPK-MB in the sera of 30 patients after thoracotomy but could detect minimal elevations, which were not thought to be significant by quantitative analysis. Pyle and associates [9] used spectrophotometric techniques to evaluate 7 patients who had undergone thoracotomy and found no evidence of CPK-MB in the serum postoperatively. Dixon and co-workers [1] evaluated both CPK and LDH changes in 20 patients after major abdominal or noncardiac thoracic surgical procedures. Elevations in serum LDH activity were noted in all patients, with LDH_4 and LDH_5 being the predominant isoenzymes Elevations of LDH_1 and LDH_2 were seen only in 1 patient who had a preoperative MI, which was confirmed at postmortem examination. The elevations in CPK noted by these authors were attributable to elevations of CPK-MM, the skeletal muscle fraction of CPK.

The changes noted in total CPK activity in the patient groups presented here agree with previously published reports in that surgical procedures generally cause elevations in total CPK activity comparable to those seen in patients with acute MIs [3, 4, 10]. One notable exception is apparent in the case of the patients undergoing bronchoscopy and mediastinoscopy. Even though these patients received preoperative medications by intramuscular injection (which usually causes elevations in serum CPK activity [3]), had general anesthesia, and had dissections of the mediastinum, their total CPK activities were not elevated beyond the established upper limits of normal.

Absolute values of CPK-MB and CPK-MB% were elevated to a significantly greater degree in those patients sustaining acute MIs. The mean elevation in this group of patients was well above the arbitrary 5% level of CPK-MB%, which cardiologists have designated as the maximal limit below which true myocardial damage is doubtful (see Fig 2, 3) [4]. Inspection of Figure 7 shows that there is some overlap between the distribution of CPK-MB% in patients having thoracotomies with the distribution of the same isoenzyme in the sera of patients with acute MIs. Clearly, 3 patients who had a thoracotomy exceeded the arbitrary 5% limit. Two others came close to but did not exceed this limit. Several factors contributed to these elevations: In 4 of the patients, long procedures requiring extensive dissection for advanced malignant or inflammatory disease had been conducted. Furthermore, these individuals were relatively young and were quite muscular. Hence, we think that the elevations may well be due to relatively extensive dissection of skeletal muscle. In the fifth patient, a clear cause for the elevation cannot be advanced since she was a relatively frail woman with an unresectable malignancy.

The changes seen in total LDH and in LDH_1 in the sera of patients sustaining acute MIs were in accord with established principles [3]. The levels of these same variables noted in the sera of the other patient groups were all significantly different. Interestingly, there was no significant difference noted in serum LDH_5 among the groups. With major operation, one would anticipate that this isoenzyme (the predominant isoenzyme of LDH in skeletal muscle) would be elevated. This certainly was not the case (see Fig 6).

Minimal overlap was noted between the levels of LDH_1 measured in the sera of patients recovering from thoracotomy and those values measured in patients with an acute MI. The 1 patient who had a serum elevation of LDH_1 that was compatible with the elevations seen after MI had no known condition that would cause such an elevation. Furthermore, she underwent a short, anterior thoracotomy for a totally benign process. Because of the demonstrated overlap of the distributions obtained from the patients sustaining MIs and those who were recovering from a thoracotomy, it appears that the careful monitoring of both enzyme systems is advisable in evaluating postoperative patients who are suspected of having acute MIs. In the majority of cases of acute MI in a patient undergoing a thoracotomy, either CPK or LDH isoenzymes would be capable of detecting the infarction without interference from any changes attributable to the operation. Monitoring of both enzyme systems in conjunction with serial electrocardiography appears to offer the best chance of confirming the diagnosis in an equivocal case.

In a practical sense, the surgeon could expect to detect virtually all MIs in patients recovering from a thoracotomy by using the following guidelines: Once MI is suspected on clinical or electrocardiographic criteria in the perioperative period, serum total and CPK-MB isoenzymes should be obtained. If the percent of CPK-MB is greater than 10% of the total CPK, there is little question that the patient has an acute MI. If the percent of CPK-MB is less than 10%, a serum total LDH and isoenzyme electrophoresis should be ordered on the second and third postoperative days. If the total LDH is elevated and the LDH_1 fraction becomes the predominant isoenzyme of LDH in the serum, the diagnosis of MI has been established.

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Perioperative Myocardial Infarction: A Diagnostic Dilemma

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ABSTRACT **Patients undergoing coronary bypass grafting were studied for incidence of perioperative myocardial infarction (MI) using three modalities: serial electrocardiograms (ECG), serial creatine phosphokinase isoenzymes (MB-CPK), and serial technetium 99m–labeled pyrophosphate scans. A definite perioperative MI was diagnosed if the results were positive in two of the three variables studied. The perioperative infarction rate for the entire group was 8%. The operative mortality was 2.9%. Seven of 8 perioperative MIs were diagnosed by the use of scanning alone. The combination of isoenzyme and ECG analysis diagnosed 5 of 8 perioperative MIs. The MB-CPK and ECG studies were associated with a higher incidence of false-positive diagnoses than myocardial scanning. Patients with perioperative MI had a benign clinical course. Justification for performing three routine ^{99m}Tc-pyrophosphate scans on all patients undergoing aortocoronary bypass operation is still to be determined.**

The rationale for myocardial revascularization is twofold: first, to relieve angina pectoris, thus improving the quality of life, and second, to preserve ischemic myocardium, thus increasing the length of life. It logically follows one must do minimal or, ideally, no damage to the myocardium during the procedure itself; otherwise, the indications for operation become limited. Reports in the literature on the incidence of perioperative myocardial infarction (MI) are numerous and have been reported to range from 8% to 35% [1–5]. The criteria for diagnosis of perioperative MI in these reports have varied. The three factors commonly used as good indicators of infarction are serial creatine phosphokinase isoenzyme (MB-CPK) analysis, serial electrocardiograms (ECG), and serial technetium 99m–labeled pyrophosphate scans (^{99m}Tc-pyrophosphate). Difficulty in interpreting these data in the patient after bypass has been reported with all of these techniques.

The importance of documentation of a perioperative MI was demonstrated well by Lim and co-workers [6]. They performed postoperative angiograms on all patients with new Q waves after aortocoronary bypass operation and found the ejection fraction to be markedly reduced. Clearly, it is important for all cardiac surgical units to have an organized protocol for diagnosis of perioperative MI to assess their techniques and results. The documentation of such an MI also will aid the clinician in the care of patients in the postoperative recovery period. At our institution, we have employed all three modalities in combination for diagnosis of myocardial necrosis. Serial ECGs, MB-CPK analysis, and ^{99m}Tc-pyrophosphate scans were done on all patients in the preoperative and postoperative periods. It is the purpose of this report to describe our experience with these modalities and discuss their interpretation in the postoperative patient.

Material and Methods

The patients included in this study represent 103 consecutive male patients who underwent myocardial revascularization from November, 1977, through July, 1978. Excluded were patients who had either left ventricular aneurysm resection or valve replacement in combination with aortocoronary bypass grafting. The patient profile of patients included in this study was as follows: average age, 57 years; ejection fraction, 61 ± 14%; left main coronary artery disease, 21 patients (3 deaths); unstable angina, 23 patients

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(3 of whom had left main coronary artery disease also); grafts per patient, 3.2 (2.3 in noncardioplegic subset); aortic clamp time, 64 ± 11 minutes.

An ECG was obtained for each patient preoperatively and postoperatively—in the immediate postoperative period and on days 1, 2, 3, and 7. All ECGs were interpreted consistently by one cardiologist (A. R. Z. M.). He was not aware of the clinical result or the results of the isoenzyme analysis or myocardial scans. The ECGs were read immediately in the postoperative period, and approximately six months after operation, they were reinterpreted. If there was any disagreement between the initial and the second reading, it was resolved in the Cardiology Department. The ECG was considered positive for a new myocardial infarction if new Q waves appeared in the postoperative period at greater than 0.04 seconds or S-T segment changes persisted for longer than 48 hours.

Creatine phosphokinase isoenzyme levels were determined on all patients using the electrophoresis method described by Rosalki [7] and Roe and co-workers [8]. Specimens were obtained preoperatively, immediately after operation, at hours 2, 4, 6, 12, 18, 24, and 30 in the postoperative period, and then daily for a week. Levels greater than 90 IU/L at any time were considered to be indicative of perioperative MI. This figure was derived by studying a separate group of patients with negative ECGs and negative myocardial scans with a benign clinical course. The mean MB-CPK level in this group was 48 ± 20 IU/L. We agree with others that in order to increase the specificity of isoenzyme diagnosis after cardiac operation, two standard deviations above the mean is the level above which a perioperative MI is highly likely [1, 9].

The ^{99m}Tc-pyrophosphate scans were done 1 day preoperatively and on days 3 and 7 postoperatively. Imaging was performed 90 to 120 minutes after the intravenous administration of 15 mCi of ^{99m}Tc-pyrophosphate. A gamma camera with a parallel-hole collimator was used. Anterior, left anterior oblique, and left lateral views were obtained for each study.

Myocardial scans were graded from 0 to 4+ [10]. Ribs and sternum served as a reference point at 2+ and 3+, respectively. Diffuse versus focal activity was recorded. The ^{99m}Tc-pyrophosphate scan was considered positive if a new region of discreet activity greater than or equal to the ribs was seen in the region of the myocardium (for example, 2+ focal uptake on the postoperative area) or if the postoperative scan showed one grade or more increase in the intensity of a previously abnormal preoperative scan (Table 1). All myocardial scans were interpreted by one of us (J. J. S.). The interpreter was unaware of the clinical course of the patient or the results of the ECG or MB-CPK analysis. Scans were reviewed twice: once in the immediate postoperative period and then again several months following discharge. Any discrepancies between the two readings were resolved in the Department of Nuclear Medicine.

A patient was considered to have sustained a definite perioperative MI if the results were positive in two of the three variables (Table 2, Groups 1 and 2). Patients who were positive in only one of the three variables under study were considered to be false positive (see Table 2, Group 3).

Seventy-five patients in this study were operated on using hypothermic cardioplegic solutions for myocardial preservation. The remaining 28 were operated on using mild systemic hypothermia at 32°C with intermittent aortic cross-clamping limited to 15-minute intervals. In general, patients requiring a lesser number of grafts were chosen for noncardioplegic arrest. The technique for cardioplegic protection of the myocardium at our institution is as follows: The patient is placed on cardiopulmonary bypass and systemically cooled to 25°C. A modified Ringer's lactate solution chilled to 4°C is injected into the aortic root through a roller pump to maintain the pressure at less than 120 mm Hg. To the Ringer's lactate solution are added the following: potassium, 30 mEq per liter, sodium bicarbonate to bring the pH to 7.6, and 50% dextrose solution to bring the solution to an osmolarity of approximately 370 mOsm per liter. The benefits of having the solution slightly alkalotic and hypertonic are well documented in the literature [11, 12]. The myocardial temperature is continuously moni-

Table 1. Patients with Uptake on Preoperative Myocardial Scan

Patient No.	No. of Grafts	CP or VF	Old MI	Unstable Angina	Preop Scan	Postop Scan 1	Postop Scan 2	Postop ECG	Postop MB-CPK
1	3	CP	+	–	3 Focal	3 Focal	1 Diffuse	–	–
2	4	CP	+	–	2 Diffuse	2 Diffuse	0	–	–
3	4	CP	–	–	2 Diffuse	4 Focal[a]	2 Diffuse	+	+
4	2	CP	+	–	3 Diffuse	2 Diffuse	2 Diffuse	–	–
5	3	CP	+	–	2 Diffuse	2 Diffuse	1 Diffuse	–	–
6	4	CP	+	–	2 Diffuse	0	0	+	–
7	4	CP	+	+	2 Diffuse	0	0	–	–
8	3	CP	+	–	2 Diffuse	Op. death	...	...	...
9	3	CP	+	–	2 Diffuse	1 Diffuse	1 Diffuse	–	–
10	3	CP	+	–	2 Diffuse	0	0	+	–
11	4	CP	+	–	2 Diffuse	0	0	–	–
12	4	CP	+	–	2 Diffuse	0	0	+	–
13	4	CP	–	–	2 Diffuse	4 Focal[a]	0	–	–
14	4	CP	–	–	2 Diffuse	0	0	–	–
15	2	VF	–	–	2 Focal	2 Focal	2 Focal	–	–
16	4	CP	–	+	2 Diffuse	1 Diffuse	0	–	–

[a] Postoperative scan considered positive.

CP = cardioplegia; VF = ventricular fibrillation; MI = myocardial infarction; ECG = electrocardiogram.

Table 2. Distribution of Patients according to Three-Factor Analysis for Perioperative Infarction

Groups	No. of Patients	New Q Waves	Mean MB-CPK (IU/L)
1. Three factors positive			
a. S+ E+ B+	4[a]	3	186
2. Two factors positive			
a. S+ E+ B–	0		0
b. S+ E– B+	3[a]		231
c. S– E+ B+	1[a]		154
3. One factor positive			
a. S+ E– B–	2		50
b. S– E+ B–	4	3	58
c. S– E– B+	9		105[b]
4. Three factors negative			
a. S– E– B–	77		46
Total	100		

[a] Definite perioperative infarction.

[b] Difference in mean MB-CPK for groups 3A and 3B compared with 3C is significant at 0.005 level (Student *t* test).

S = myocardial scans; E = serial electrocardiograms; B = MB-CPK isoenzyme levels.

tored with a probe in the lateral wall of the left ventricle.

Initially, we inject enough cardioplegic solution to bring the myocardial temperature down to 8° to 12°C. The temperature is maintained with a mixture of frozen and chilled saline solution in the pericardium. Cardioplegia is reinstituted after each distal anastomosis to keep the myocardial temperature ideally at 15°C throughout the procedure. The average amount of cardioplegia used per patient is 1,400 ml ± 450. Lasix (furosemide) was given in the oxygenator as necessary in order to prevent massive hemodilution.

When noncardioplegic arrest is used, the systemic temperature is reduced to 32°C. The aorta is clamped for 10- to 15-minute intervals to perform the distal anastomosis. The clamp is then removed, and the heart is allowed to beat for 5 minutes in order to pay back the oxygen debt before the next distal anastomosis is begun.

Results

There were 3 deaths in this series of patients. All 3 patients had significant left main coronary artery obstruction. Two were operated on using cardioplegic arrest and the other, with intermittent cross-clamping. This study is retrospective and nonrandomized; therefore, the cardioplegic group cannot be compared with the noncardioplegic group of patients.

Employing three modalities for a diagnosis of perioperative MI provides eight possible subsets of patients (see Table 2). Four patients were positive in all three variables, and another 4 patients were positive in two of the three, giving a rate of perioperative MI of 8% for the entire series. All infarcts occurred in the cardioplegic group, thereby reflecting the advanced coronary obstruction in this subset. None of these 8 patients had left main obstruction or unstable angina. The 8% rate excludes the 3 operative deaths for which perioperative MI is not a diagnostic problem. One patient who sustained a perioperative MI had a prolonged hospitalization and an episode of heart failure. The remainder had a smooth recovery and were discharged after 10 days. In only one of these 8 patients was the scan negative. On the other hand, 2 patients whose MB-CPK levels and ECG data were negative had positive scans. We interpret this as a 2% false-positive result by use of myocardial scanning alone. Nine patients in this study had significant ECG changes (6, Q waves; 3, prolonged S-T segment changes) after operation. However, 4 had a negative scan and negative analysis of MB-CPK levels (3, new Q waves). Nine patients had MB-CPK levels greater than 90 IU/L with negative ECG and negative scan (see Table 2, Group 3C). The combination of positive enzyme analysis and positive ECG diagnosed 5 of 8 perioperative MIs. Table 3 illustrates the sensitivity, specificity, and predictability of all three modalities.

Table 3. Sensitivity, Specificity, and Predictability of the Three Modalities

Modality	Scan	ECG	MB-CPK	ECG + MB-CPK
Sensitivity[a]	0.88	0.63	1	0.625
Specificity[b]	0.98	0.96	0.90	1
Predictability[c]	0.78	0.55	0.47	1

[a] Sensitivity [37] = true positive/(true positive + false negative).
[b] Specificity [37] = true negative/(true negative + false positive).
[c] Predictability [37] = true positive/(true positive + false positive).

Sixteen patients in this study had preoperative myocardial scans interpreted as being positive at the 2+ level or above (see Table 1). Eleven of these patients (69%) had previous myocardial infarctions to account for this uptake. Two patients had a positive scan in the postoperative period (Patients 3 and 13). In Patient 3, a perioperative MI was confirmed by MB-CPK analysis and ECG. The other patient had a negative ECG and negative MB-CPK levels. In 8 patients, the scan reverted to negative in the postoperative period. One patient remained unchanged, and in the remaining patients, major improvement was noted on the second postoperative scan. In this group of 16 patients, only 2 were operated on for unstable angina. All patients, except for Patient 8, who died in the operating room, had an uneventful and uncomplicated postoperative course.

Comment

The clinical significance of perioperative MI was questioned in 1978 by Spencer [13]. Others have shown decrease in ejection fraction in patients with documented perioperative MI [14]. Obviously, if one accepts minimal elevation of isoenzymes or all new Q waves to be diagnostic of perioperative MI, then the clinical importance of all perioperative MIs would be reduced due to a high incidence of false-positive diagnoses. It is therefore important to have an accurate method of diagnosing cell death after revascularization operations as a guideline for improving surgical techniques and intraoperative myocardial protection.

Diagnosis by ECG of perioperative MI after cardiac operation, especially myocardial revascularization, is extremely difficult. In 1975, Gerrard-Gough and colleagues [15] reported that an S-T segment elevation in the postoperative period was an unreliable indicator of perioperative MI because only in a small percentage of patients did the S-T segment changes persist over a 48-hour period. In our interpretation of the ECG, we also used this criterion (3 patients). Electrolyte imbalance, fluid shifts, and pericarditis have been shown to affect S-T segment changes within the first 48 hours after operation [16].

There are several reports that claim an 8% incidence of false-positive new Q waves in the postoperative ECG after aortocoronary bypass operation [17, 18]. This phenomenon is explained as an unmasking of old infarcted areas by the newly revascularized myocardium. Assad-Morell and associates [19] reported a 12% incidence of perioperative MI diagnosed by ECG criteria alone. They did not consider new Q waves to be a false-positive result and disputed the theory of possible false-positive Q waves after revascularization. In our series, 3 patients had new Q waves after operation and negative MB-CPK levels and negative myocardial scans. This seems to support the previous reports of false-positive Q waves although our incidence is less than that previously reported. All 3 of our patients had very benign postoperative courses.

The MB-CPK values have proved to be of great help in the diagnosis of perioperative MI [20]. Dixon and colleagues [21] in 1973 showed that elevated MB-CPK levels correlated well with ECG changes indicative of acute myocardial infarction in the postoperative patient. They reported infarction rates of 21% after aortocoronary bypass operations. Seven percent of their patients showed elevated MB-CPK levels with negative ECGs. This is less than our series in which 12 patients had elevated MB-CPK levels (90 units) with negative ECG readings (see Tables 2, 2B, 3C).

In 1977, Dhanani and associates [22] pointed out that after a general thoracic operation, 40 to 50% of patients will have mild to moderate elevation of MB-CPK levels. Others have shown this to be even higher after cardiac procedures in patients with negative ECGs and a benign clinical course [4]. Klausner and co-workers [23] demonstrated that in patients with negative scans and negative ECGs after aortocoronary bypass, the mean MB-CPK level was 53 units compared with 115 units in patients with positive scans and positive ECGs in the postoperative period. It is apparent that each clinical laboratory should establish a value for MB-CPK levels after cardiac operation above which a diagnosis of perioperative MI is highly specific and is not due to cardiac manipulation, blood hemolysis, pulmonary damage, or defibrillation, all of which are known to produce elevation in MB-CPK [21, 24]. Nine patients in our study had MB-CPK levels diagnostic of perioperative MI, but their ECGs and myocardial scans showed no changes, thus making the diagnosis of subendocardial infarction unlikely (see Table 2, Group C). This accounts for a 9% false-positive diagnosis. Analysis of MB-CPK as the sole criterion for diagnosis of perioperative MI has a low predictive value. Those who argue that the presence of MB-CPK represents subendocardial necrosis cannot explain the lack of ECG or myocardial scanning findings to support this diagnosis.

In 1974, the laboratory work of Bonte and colleagues [25] showed that the ^{99m}Tc-pyrophosphate ion accumulates in the necrotic myocardial cells. This work stimulated a large amount of clinical and laboratory investigation. The necrotic myocardial cells are permeable to calcium ion, which, together with the technetium ion, is precipitated in the damaged mitochondria of the cell, thus yielding a positive scan [26]. This phenomenon occurs within the first 12 to 17 hours after infarction. It also has been shown that this deposition of calcium ion occurs only in irreversibly damaged cells and not in ischemic cells [27].

The importance of a myocardial scan with a 2+ diffuse uptake is still in debate, especially in the setting of unstable angina. In this study, 14 patients had 2+ diffuse uptake or greater preoperatively and 2 had focal uptake (see Table 1). Poliner and co-workers [28] stated that a 2+ diffusely positive scan is indicative of subendocardial infarction and proved it in patients examined postmortem. His group and others use this to argue that a myocardial scan will differentiate patients with unstable angina from those with subendocardial infarction [29, 30]. This finding, however, is difficult to accept since it has been shown that 14% of the population without coronary disease will have 2+ diffusely positive myocardial scans [31]. Donsky and associates [32] reported that one-third of patients with unstable angina will have a 2+ myocardial scan with diffuse uptake. Karunaratne and colleagues [33] showed a 40% incidence of 2+ diffusely positive scans in patients with unstable angina with negative ECGs and MB-CPK levels. In this series, only 2 patients of 23 with unstable angina had a preoperative positive scan (see Table 1). We are unable to explain this low incidence. No patient listed in Table 1 had preoperative ECG changes or MB-CPK elevation compatible with subendocardial infarction. This supports those who believe that only localized uptake is of clinical importance although microscopic cellular death cannot be excluded.

Only 1 of the patients with preoperative uptake on the myocardial scan had a complicated postoperative course (Patient 8). Whether myocardial uptake on the preoperative scan represents unstable angina, subendocardial infarction, or old myocardial infarction (11 patients), such patients do not appear to be at any greater risk for aortocoronary bypass operation (ECG and MB-CPK analysis, negative). Without the aid of preoperative scanning, Patients 1 and 15 would have been diagnosed as probable perioperative MI with positive myocardial scans. Therefore, if a positive myocardial scan is to be used as a criterion for perioperative MI, scanning must be done routinely preoperatively as well as postoperatively.

The rate of perioperative MI among patients surviving operation in this series is 8%. All infarctions occurred in patients operated on using hypothermic cardioplegic solution for myocardial protection. These patients required more grafts and had poorer ventricular function than the patients operated on without cardioplegia. Five of 8 infarctions were diagnosed without the use of myocardial scanning. This is in agreement with reports by Willerson [34], Platt [35], and their associates, which show that scanning diagnoses twice as many infarctions as ECG or MB-CPK analysis.

In conclusion, the diagnosis of perioperative MI is a difficult one. Of the three modalities studied, myocardial scanning with ^{99m}Tc-pyrophosphate appears to have the highest specificity and predictability. It is particularly suited for those patients with bundle-branch block and old myocardial infarction on the ECG [36]. It also appears to eliminate problems encountered in the interpretation of MB-CPK data, such as hemolysis, heart failure, pulmonary damage, and myocardial manipulation. One cannot rely solely on enzyme data or ECG data for the accurate diagnosis of perioperative MI in the patient who has undergone aortocoronary bypass operation. The clinical importance of small perioperative infarctions however is still in debate. Whether patients with minimal MB-CPK elevation or 2+ localized scans will have reduced ejection fraction in the follow-up period has not been shown. The cost-effectiveness of performing three myocardial scans in all patients undergoing aortocoronary bypass remains to be determined.

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The Effect of Metastasectomy: Fact or Fiction?

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ABSTRACT **Metastasectomy in the treatment of solitary metastases has been recommended almost unanimously. The basis for this recommendation has been that 5-year survival after metastasectomy is around 30%, which is just as good as after operation for bronchial carcinoma. It has been assumed, implied, or claimed that the 5-year survival without operation is nil. Control material is, however, lacking.**

Seventy surgically treated patients were compared with a small, historical control group of 12 patients. There was no difference in 5-year survival. Because of these findings and after a study of the literature, we postulate that patients with lung metastases fulfilling the criteria for operation constitute a selected group with a favorable natural history. Five-year survival, therefore, is an insufficient way of describing the effect of metastasectomy. However, patients with 10-year survival are rare in the literature.

In some patients with a favorable tumor-host relationship or with possibilities for effective chemotherapy, cure or prolongation of life has been achieved. Such patients should undergo operation. Randomized studies are needed in all groups for which we do not have sufficiently strong evidence that metastasectomy contributes to the longevity of the patient.

The treatment of solitary metastases in the lungs during the last decades has most often been surgical. In reports comprising a total of more than 2,500 patients who underwent operation [3, 5, 6, 8–11, 13–17, 19–21, 24–27, 29, 31, 33; see especially 5], surgical removal of the metastasis was more or less unanimously recommended. In connection with an analysis of our own surgically treated series of patients, we scrutinized the literature and found to our surprise that there is a striking lack of scientific basis for this recommendation, in particular, as there have been no nonoperated control groups for comparison. The basis of the recommendation of operative treatment in these patients has been mainly that the 5-year survival after metastasectomy is about 30%, and that the results are just as good as after operation for bronchial carcinoma.

The aim of this article is to show that these two arguments are not sufficient evidence of the superiority of surgical treatment in these patients, to question the value of metastasectomy, to define the indications for operation more clearly, and to demonstrate the need for randomized studies of large groups among the patients now undergoing operation.

Material

Surgically Treated Patients

Between 1961 and 1978, 70 patients underwent operation at the Department of Thoracic Surgery of the University Hospital, Uppsala, for solitary lung metastases. The criteria for surgical treatment were as follows:

1. The primary tumor was radically removed or curatively treated by other means.
2. No metastases were found in organs other than the lung.
3. Only one lung was involved (exception: 1 patient with osteosarcoma).
4. The patient was operable according to the current norms for elective lung operation.

The survival of the patients was studied from the medical records and the national population register and analyzed by the actuarial method described by Andersson and associates [1]. The survival rate was calculated up to June, 1979, inclusive, whereby the shortest observation period was six months.

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Controls

During the period 1937 to 1964, 91 patients with tumors of the lung that were found to be metastases were treated at the Department of Lung Medicine of the University Hospital, Uppsala [22]. Four of these patients were operated on and are included in the surgically treated group. At a renewed analysis of the records of these 91 patients, we found a further 12 patients who fulfilled the present criteria for operation but in whom, according to the norms of that time, operation was not performed. Some of these patients received radiotherapy.

Table 1. Diagnosis in Surgically Treated Patients with Lung Metastases

Primary tumor	No. of Patients
Renal carcinoma	30
Sarcoma	9
Malignant melanoma	8
Gastrointestinal carcinoma	8
Breast carcinoma	4
Carcinoma, cervicis uteri	4
Miscellaneous	7
Total	70

Results

Preoperative data for the surgically treated and control groups are given in Tables 1 and 2. The thirty-day mortality was 1.4% (1 patient). The number of operations in the different years can be seen in Figure 1. The survival curves for the two groups are shown in Figure 2. In the surgical group the calculated 5-year survival was 31%, and in the controls the absolute 5-year survival was 25%. The calculated 7-year survival in the surgical group was 17%, and the absolute 7-year survival in the controls was 0. This difference is not statistically significant.

The surgical group was analyzed further. In 40 patients the metastasis was solitary, and in the other 30 there were multiple metastases (Fig 3). The calculated 5-year survivals for these two groups were 37% and 23%, respectively. The difference is not statistically significant. When two factors—time interval between the primary operation and the metastasectomy, and multiple or solitary metastases—were combined (Fig 4), no significant differences were found, although the slopes of the curves differed. Survival curves are also presented for the three largest diagnostic groups—renal cancer (hypernephroma), malignant melanoma, and sarcoma (Fig 5). In this surgical group, patients with malignant melanoma had the poorest prognosis.

Table 2. Clinical Data on 12 Unoperated Patients with Solitary Pulmonary Metastases

Patient No.	Age At Diagnosis (yr)	Diagnosis	Interval from First Operation to Diagnosis (yr)	Survival after Diagnosis (yr)
1	56	Breast carcinoma	10	4
2	41	Breast carcinoma	7	5.3
3	22	Spindle cell sarcoma	4.1	5.9
4	60	Breast carcinoma	9	6.5
5	48	Uterine myosarcoma	3.3	1
6	50	Renal carcinoma	5	2.5
7	61	Colonic carcinoma	2.6	3.8
8	58	Renal carcinoma	5	2.7
9	61	Uterine carcinoma	8	2
10	79	Uterine carcinoma	10	0.5
11	33	Round cell sarcoma	2.3	0.9
12	72	Breast carcinoma	2.5	5

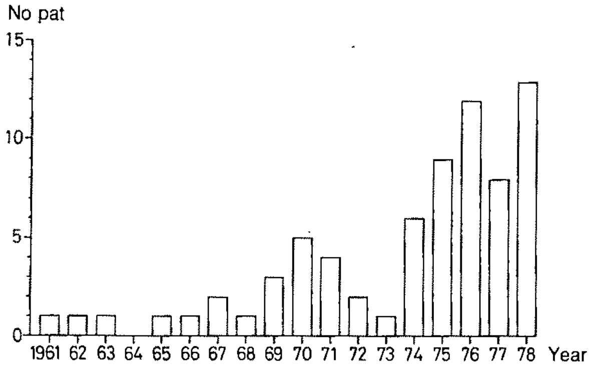

Fig 1. Number of metastasectomies according to year of operation.

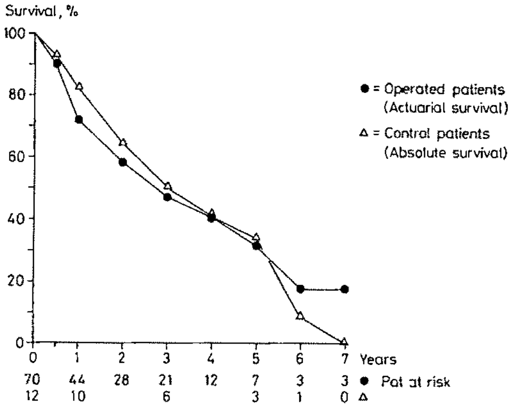

Fig 2. Survival after metastasectomy or diagnosis in 70 operated and 12 control patients.

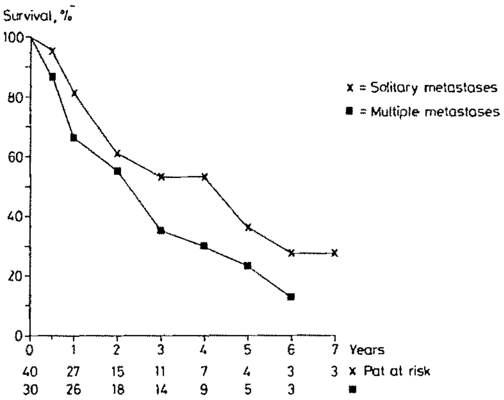

Fig 3. Survival after metastasectomy in patients with solitary and multiple lung metastases.

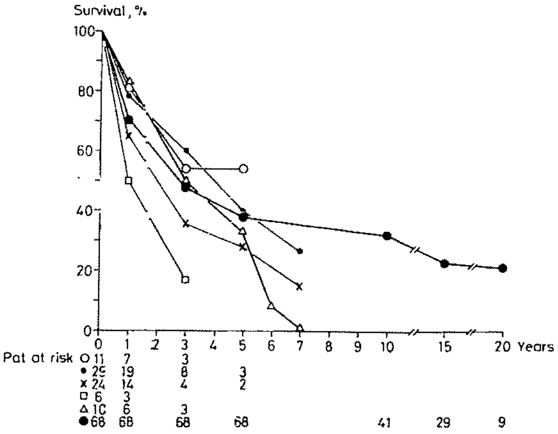

Fig 4. Survival after metastasectomy or diagnosis in present study and in that of Turney and Haight [29]. △ = nonoperated patients; • = interval between operations 1 and 2 > 1 year, solitary metastases; X = interval between operations 1 and 2 > 1 year, multiple metastases; ○ = interval between operations 1 and 2 < 1 year, solitary metastases; □ = interval between operations 1 and 2 < 1 year, multiple metastases; ● = patients of Turney and Haight, recalculated.

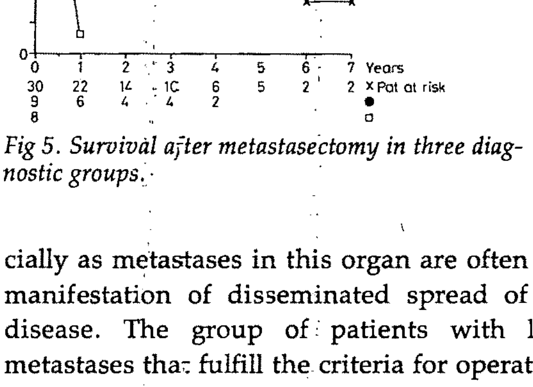

Fig 5. Survival after metastasectomy in three diagnostic groups.

Comment

When evaluating different methods of treatment, it is often found that there is a lack of knowledge about the natural history of the disease. It is known that the appearance of lung metastases is a very poor prognostic sign, especially as metastases in this organ are often one manifestation of disseminated spread of the disease. The group of patients with lung metastases that fulfill the criteria for operation, i.e., the primary tumor under control, no other metastases discovered, and only one lung involved, probably comprises a selected group with a benign tumor biology. The natural history of such a group has not been sufficiently well elucidated. A scrutiny of the surgical literature concerning lung metastases has shown that the question of a control group or of knowledge about the natural history has only been touched upon briefly and incidentally. It has been assumed, implied, or claimed that 5-year survival without operation is nil.

In another analysis of patients with lung metastases seen at this hospital [22], it was found that of 91 patients diagnosed at the Department of Lung Medicine during the years 1937 to 1964, there were 12 nonoperated patients who fulfilled the present criteria for operability and would have had an operation. We therefore have access to a small and historical control group with whom the results of the surgically treated patients can be compared. It is clearly evident from Figure 2 that the nonoperated 12 patients had a relatively good prognosis. The absolute 5-year survival was 25% (3 patients out of 12). The longest survival time was 6.5 years. From this small group it can be concluded that the natural prognosis in this selected group is probably considerably better than in patients with lung metastases who do not satisfy the criteria for operation.

In the light of this conclusion, the results in the group who had surgical treatment immediately become more doubtful. It is quite clear that operation for metastasis does not give the good result suggested by the 30% 5-year survival. The promised results for metastasectomy must be formulated with more caution. Moreover, further investigations are necessary.

The representativeness of our small control group may be doubtful. It is historical, which means that the selection mechanisms certainly differed from those of today. The composition of the group deviates somewhat from what is normally seen in surgical groups with lung metastases. The average interval between the primary tumor operation and the discovery of the metastasis was 5.5 years, which is long, a fact that has been stated to be prognostically favorable. Yet another factor to be considered is that these 12 patients were collected during a 28-year period, which implies a mean frequency of 1 patient every other year. This is in sharp contrast to the situation today; during the last years between 8 and 13 patients have been operated on annually. It is possible, therefore, that this control group may comprise a very selected group of patients with tumors with an unusually benign clinical course—a group more selected than today's surgical groups. However, this finding does not mean that the results from the control group should not be taken into account seriously when the value of surgical removal of lung metastases is being discussed.

The presented results show that there was no difference in survival between the surgically treated series and the control group up to 7 years after diagnosis of the metastasis. After 7 years, 3 patients were alive in the surgical group but none of the controls were alive. Therefore, surgical treatment would seem justified. It is seen in Table 2, however, that in the control group the interval between the primary cancer operation and the diagnosis of lung metastases was long. It would seem highly possible that the diagnosis of metastasis could have been made earlier, by several years in many patients. Earlier diagnosis would have meant that the length of survival after diagnosis would have increased correspondingly. The whole survival curve for the control group would have been shifted upward and, theoretically, survivals of 7.8 and 9 years could have been achieved. There is, therefore, a need to raise the demand for long-term follow-up for surgically treated patients to 10 years. However, the patients with 10-year survival presented in the literature are too few and too incompletely reported to permit any definite conclusions to be drawn concerning the frequency of cures.

Van Dongen and co-workers [30] summarized their impression of the value of metastasectomy after a thorough study of the literature (180 references). They demonstrated a positive basic attitude toward operation, but considered 3-year and 5-year survival rates insufficient as a reliable indication of cure. They supported this view by pointing out the many reports of patients who attained 5-year survival but showed signs of residual disease. On this basis, they stated that the percentage of real cures appears to be considerably lower than the 30% 5-year survival implies.

Turney and Haight [29], however, reported a group with a truly long-term follow-up. They described 68 patients who were followed for at least 5 years, 9 of them for 20 years (see Fig 4). Among these 68 patients, the 10-year survival was 32% (13 out of 41), the 15-year survival was

28% (8 out of 29), and 2 patients of 9 survived more than 20 years. The authors also provided evidence of a real cure in some patients who lived for a long time after the metastasectomy, died of another disease, and at postmortem examination showed no signs of residual malignancy. Their findings must be regarded as proof that metastasectomy can result in a real cure.

A more thorough scrutiny of their patient group, however, reveals that it is extremely selected. Only 2.7 patients per year were being operated on at this large center, which was early considered a mecca for metastasectomy. The average interval between the primary tumor operation and the diagnosis of metastasis was 5.5 years; the interval between this diagnosis and metastasectomy is not reported. Their material consisted mainly of uncommon malignant tumors with a relatively unknown natural history. Only 40% were carcinomas, while 52% were sarcomas and 8% were miscellaneous. Four patients had histologically benign tumors that had nevertheless metastasized. However impressive the long-term survival may be, it proves nothing more than that cures after metastasectomy can occur in a very well selected group. It provides no scientific justification for more general use of metastasectomy in solitary, multiple, or bilateral lung metastases.

The question of the natural history of malignant diseases and the possible effect of metastasectomy can also be illustrated by the following reasoning: the frequency of patients with lung metastases who fulfilled the criteria for operation was 11.8% in the study of Fallon and Roper [6] and 14.5% in our nonoperated series. According to Turner and Jaffe [28] and Willis [32], 22 to 30% of patients who die of malignancy have metastases in the lung. Assuming that this percentage is the same, or certainly no greater before death, it may be calculated that at most 2.6 to 4.3% of all malignant tumors should satisfy the criteria for operation. This figure corresponds relatively well with the finding of Minor [18] that 1.2% of patients with malignancy have solitary metastases in the lungs at some time during the course of the disease. Of these patients, 30% would survive for 5 years as a result of or in spite of an operation, which amounts to about 0.4% of all patients with malignant tumors. But in the natural history of malignant diseases, a spontaneous 5-year survival of 0.4% is not unusual. Riches [23] reported a series of 443 totally untreated patients with renal carcinoma deemed inoperable because of the extent of the tumor or another condition precluding operation. The crude survival was 4.4% at 3 years and 1.7% at 5 years.

A serious attempt to shed light on the dependence of survival upon the biological properties has been made by Morton and his group [8, 9, 13, 19]. They calculated the tumor doubling time (TDT) according to Collins and associates [4] in nonoperated and operated patients with lung metastases. In the group with a short TDT (less than twenty days), all patients had died after eighteen months. When TDT was between twenty and forty days, all nonoperated patients had died after eighteen months and all operated patients after thirty months. When it was more than forty days, all nonoperated patients had died after twenty-four months, while in the operated group there was a 5-year survival of 63%. The prognosis was independent of whether the patient had multiple or bilateral metastases. These findings have been confirmed by some authors [10, 11, 21, 26], but refuted by others [2, 7]. It is evident from the reports of Morton's group [8, 9, 13, 19], however, that the reason why the nonoperated patients had not undergone operation was that they did not fulfill the criteria for operation; probably a decision was made against operation because of metastases in other organs. Thus, very good results are obtained in patients who have demonstrated the benign nature of their tumors by the presence of metastases in no other organ except the lung and by an extremely low rate of tumor growth. It is reasonable to assume that among these patients some really will be cured. The combined results of the studies of Turney and Haight [29] and Morton and colleagues [8, 9, 13, 19] are so convincing that from a practical viewpoint the indications for operation must be regarded as absolute in patients with metastases with a slow tumor growth.

One of the few diseases for which an adequate control group is available is osteosarcoma metastases. Since as many as 80% of all osteosarcomas send metastases to the lungs and since all these lung metastases are operated on today, it may be said that for this disease, the total material is so complete that comparison with earlier nonoperated patients can be made [8, 10, 12, 25]. However, there is reason to speculate on whether it is not the concomitant chemotherapy that has brought the greater part of the prolonged survival times after operation for osteosarcoma metastases [25]. Nevertheless, in this and other malignancies in which there are possibilities of combined treatment with effective or semieffective chemotherapy and operation, there seems to be such strong evidence of an effective therapy that operation would appear indicated [2, 5].

The results from our study cannot be taken as evidence that metastasectomy is an unnecessary operation. However, we did find the following:

1. Patients who fulfill the criteria for lung metastasectomy probably comprise a selected group with a particularly benign tumor-host relationship.
2. It is misleading to express the value of metastasectomy as having 30% 5-year survival as a proportion of those surviving 5 years will subsequently die of their malignancy.
3. A follow-up period of at least 10 years must be demanded in a scientific evaluation of metastasectomy material.
4. A few patients with a benign tumor appear to be curable by metastasectomy.
5. Further studies are necessary to define the general role of metastasectomy more exactly in the treatment of lung metastases.
6. To settle this matter, randomized studies are needed in all groups for which we do not have sufficiently strong evidence that metastasectomy contributes to the longevity of the patients.

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Pulmonary, Mediastinal, and Cardiac Presentations of Histoplasmosis

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ABSTRACT **Sixty-one patients with histoplasmosis were identified. They ranged from 14 months to 67 years old. There were 56 male and 5 female patients. Disease presentations were categorized into pulmonary (47), mediastinal (11), pericardial (2), and cardiac (1). Twenty of the patients with pulmonary involvement had histoplasmomas treated by wedge resection (18) or lobectomy (2). Twenty-two of the 27 cavitary lesions were treated by lobectomy and 4 by segmental resection, and 1 required pneumonectomy. The patients with mediastinal granulomas or fibrosis underwent exploration for diagnosis and curative or palliative procedures. Two patients with pericardial histoplasmosis required pericardial windows to relieve acute tamponade. One patient with disseminated histoplasmosis required aortic valve replacement for histoplasmosis valvulitis with severe regurgitation. The 1 operative death was a patient requiring pneumonectomy for mediastinal histoplasmosis.**

Indications for operative intervention in pulmonary histoplasmosis included resection of a new or enlarging pulmonary nodule to provide a definite pathological diagnosis and resection of persistent thick-walled pulmonary cavities. Mediastinal granuloma with or without fibrosis required exploration for diagnosis, palliation, or cure. Fungal endocarditis necessitated treatment with amphotericin B and valve replacement to stabilize the patient's hemodynamic status and prevent embolization of large fungal vegetations. Pericardial effusion, a rare manifestation of histoplasmosis, was seen as acute tamponade requiring emergency intervention.

Vanderbilt Medical Center has played a major role in the diagnosis and delineation of the natural history of histoplasmosis. DeMonbreun, Christie, Diveley, McCracken, and Goodwin have all helped to outline the approach to this disease. In this update of Vanderbilt's clinical and pathological experience, we have viewed histoplasmosis infection in terms of a unified concept because we believe infection in endemic areas is universal and usually asymptomatic. The manifestations represented in this paper are the abnormal host responses to this endemic fungus with a variety of organ systems affected. They are examples of the structural defect present in chronic pulmonary histoplasmosis, the immune defect of disseminated histoplasmosis, and the unique host response occasionally seen to healed primary infections such as mediastinal fibrosis or an enlarging histoplasmoma [9].

Materials and Methods

The charts of all patients requiring operation for bacteriologically or pathologically confirmed histoplasmosis at Vanderbilt University Affiliated Hospitals between 1960 and 1978 were reviewed. Only those patients whose bacteriological specimens revealed *Histoplasma capsulatum* or whose pathological specimen confirmed the organisms were included in the study. Sixty-one such patients were identified. The age of the patients ranged between 14 months and 67 years; there were 56 male and 5 female patients. Disease presentations were divided into the anatomical area affected, and symptoms were dependent on the area involved. Of the 61 patients, 47 had pulmonary involvement. Mediastinal histoplasmosis was found in 11 of the 61 patients. Pericardial histoplasmosis was diagnosed in 2, and 1 patient had aortic valvulitis secondary to disseminated histoplasmosis.

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Symptoms in 47 Patients with Pulmonary Histoplasmosis

Symptoms	Cavitary Lesions (27 Patients)	Pulmonary Nodule (20 Patients)
Pneumonia	6	
Malaise	6	
Night sweats	3	1
Sputum production	3	1
Dyspnea	3	
Fever	6	2
Hemoptysis	5	1
Cough	12	8
Weight loss	7	2
Asymptomatic	5	10

Of the 47 patients with pulmonary involvement, 27 were operated on because of cavitary lesions secondary to chronic pulmonary histoplasmosis. Symptoms in these patients included chronic cough, chronic bronchitis, weight loss, fatigue, and hemoptysis (Table). The other 20 patients underwent exploration for a solitary pulmonary nodule which, on pathological examination, proved to be a histoplasmoma. These patients were explored because of a new nodule on chest roentgenogram or an obviously enlarging one. Half of these patients were asymptomatic.

Mediastinal histoplasmosis was diagnosed in 11 patients. This group was seen with atelectasis, pneumonia, and respiratory symptoms in the face of an abnormal chest roentgenogram.

Two patients were found to have histoplasmosis pericarditis and underwent pericardial resection for signs of congestive heart failure with elevated central venous pressure and pericardial effusion. Both of the patients were febrile, appeared systemically ill, and had chest pain.

One patient with previously diagnosed aortic valve insufficiency had disseminated histoplasmosis, histoplasmosis endocarditis, and aortic valvulitis. Florid congestive heart failure requiring vigorous therapy rapidly developed. Following 2 gm of a 4 gm course of amphotericin B, the patient underwent aortic valve replacement.

Results

Pulmonary Histoplasmosis

Twenty-seven patients with cavitary histoplasmosis underwent operation. Twenty-two were treated by lobectomy and 4 by segmental resection, and 1 required pneumonectomy. Three patients required thoracoplasty because of an empyema following lobectomy. The pneumonectomy was necessary because of extensive mediastinal inflammatory disease as well as cavitary upper lobe disease in a patient with massive hemoptysis. There were no operative deaths in this group.

Follow-up has been obtained in 23 of the 27 patients with follow-up ranging from one year to fourteen years. Recurrent cavitary disease developed in 5 patients, 2 of whom were treated with a 2 gm course of amphotericin B. No patient in this group underwent a second operative procedure because of concurrent chronic obstructive pulmonary disease and marginal respiratory reserve.

Ten patients in this group had signs and symptoms of obstructive pulmonary disease which compromised their activity level. There was no documented recurrent disease in this group, and the majority of the patients had severe chronic obstructive pulmonary disease. Bronchogenic carcinoma developed in 1 patient who was then lost to follow-up, as were 4 other patients. There were 2 deaths during the follow-up period; one was due to a myocardial infarction and the other, to progressive respiratory insufficiency. Five patients with cavitary histoplasmosis were found to be doing well and were essentially asymptomatic.

Twenty patients underwent exploratory thoracotomy for a solitary pulmonary nodule. Eighteen were treated by wedge excision, and 2 underwent lobectomy. Three of these patients have been lost to follow-up during the eighteen-year period. No cavitary pulmonary disease develcped in the other 17 patients.

Mediastinal Histoplasmosis

Eleven patients were found to have mediastinal histoplasmosis. Seven had mediastinal fibrosis, and 4 underwent exploration for noncalcified enlarging mediastinal nodes that proved to have *Histoplasma capsulatum* present. All of the patients with mediastinal fibrosis had pathological evidence of *Histoplasma* organisms.

In the group of 7 patients with mediastinal fibrosis, 4 required pneumonectomy for massive hilar fibrosis with atelectasis and pneumonia, and 1 underwent two attempts at superior vena cava enlargement. Two patients underwent diagnostic exploration without mediastinal or pulmonary resection. There was 1 death in the group having pneumonectomy. The patient who died was a 57-year-old man in whom an empyema and bronchopleural fistula developed after pneumonectomy. The 3 remaining patients were doing well at two to seven years postoperatively. One patient had two attempts at superior vena cava enlargement–replacement over a seven-year period and was lost to follow-up two years after the second operation. Two patients were explored for diagnosis and found to have fibrotic masses. One was placed on a regimen of amphotericin B for an unknown time for extrinsic compression of the left main bronchus and was asymptomatic five years later. The other patient was found to have fibrosis surrounding the superior vena cava and azygos vein and was asymptomatic without treatment two years later.

Four patients underwent exploration for enlarging noncalcified mediastinal nodes. One patient in this group underwent a right middle lobectomy for persistent pneumonia and atelectasis secondary to enlarging mediastinal nodes laden with *Histoplasma capsulatum*. The remaining 3 underwent diagnostic exploration for granulomas. All of these patients were asymptomatic without obvious recurrence or signs of fibrosis at one to four years.

Pericardial Histoplasmosis

Two patients underwent left thoracotomy, lymph node biopsies, and pericardial drainage procedures for acute fibrinous pericarditis and pericardial effusion. On pathological examination, both were found to have *Histoplasma capsulatum* in the pericardium and surrounding hilar lymph nodes. One patient was lost to follow-up, and the second is doing well without pericardial calcification one year postoperatively. The second patient was treated with amphotericin B.

Valvular Histoplasmosis

One patient, a 55-year-old man with preexisting aortic regurgitation, was seen with disseminated histoplasmosis and histoplasma endocarditis. Because of refractory congestive heart failure secondary to progressive aortic insufficiency, and a large valvular vegetation, the patient underwent valve replacement with a size 25 Björk-Shiley valve. Postoperatively the patient completed his 4 gm course of amphotericin B and was doing well, without valve dysfunction or evidence of histoplasmosis, one year postoperatively.

Comment

Vanderbilt University Medical Center has been intimately involved in deciphering the manifestations of infection with the soil fungus, *Histoplasma capsulatum*. Following Samuel T. Darling's [5] initial description of this fungus in 1905, W. A. DeMonbreun [6], a pathologist at Vanderbilt, extensively reviewed the available information on *Histoplasma capsulatum*. He proved, following his isolation of the organism, that the etiological agent in the infections noted by Dr. Darling and others was a fungus. In the 1960s and 1970s, Drs. Goodwin, Snell, and Des-Prez [10–12] of the Department of Medicine at Vanderbilt compiled several reviews on mediastinal and pulmonary aspects of the disease as well as a collective review of histoplasmosis seen at Vanderbilt. From Vanderbilt's surgical sphere, Drs. Diveley and McCracken [8] in 1966 presented a review of the operative resection of 29 cases of cavitary pulmonary histoplasmosis seen at Middle Tennessee Chest Disease Hospital. The present review of eighteen years of clinical, pathological, and roentgenographic experience with histoplasmosis is built on the information acquired by many of these people

Infection with the dimorphic fungus *Histoplasma capsulatum* as demonstrated by histoplasmin skin reactivity is virtually endemic in the middle parts of Kentucky and Tennessee [4]. Human infection is initiated by inhalation of the airborne spores, and the lung is the site of primary infections as well as reinfections [9]. Infection in normal populations is usually asymptomatic. However, Goodwin and co-workers [11] believe that the patient with pulmonary histoplasmosis is unique because of the "conspicuous presence of emphysematous and bullous spaces." It is thought that in cavitary disease there initially has been an inflammatory response to soluble antigenic substances followed by eventual tissue necrosis occasionally accompanied by fibrosis. Twenty percent of patients in whom pulmonary histoplasmosis develops follow this route [11].

In our series, as in other reports of cavitary pulmonary histoplasmosis, cavitary lesions were seen in older individuals; 24 of the 27 patients were older than 40. The cavities, as noted by Levene [13], Saab [15], and their co-workers, were usually located in the upper lobes, which lends support to the premise that the disease occurs in emphysematous lung tissue. The majority of symptoms in cavitary disease were related to the respiratory tract and infection. Operative intervention is indicated in those patients who have large, thick-walled cavities (3 to 4 mm thick), relentless respiratory symptoms, and no improvement after one or two courses of amphotericin B, 1 to 2 gm each [3]. Many of these thick-walled cavities, if unoperated on, progress 1 to 2 cm a year and are a source of persistent infection. These patients are subject to fibrosis secondary to episodic aspiration of cavity contents and eventual progressive respiratory insufficiency [11]. Those cavities that are thin-walled (< 2 mm) are less likely to harbor persistent infection or to lead to fibrosis secondary to aspiration and therefore are usually treated with amphotericin B alone. In this series of 27 patients with cavitary disease there was no operative mortality and minimal morbidity, results justifying an aggressive operative approach to patients with thick-walled cavitary disease who are unimproved by therapy with amphotericin B.

Twenty patients in this series underwent exploration for a solitary pulmonary nodule. Indication for exploration was the necessity to establish a definitive diagnosis, and the explorations were carried out without mortality or significant morbidity. Eighteen of the 20 patients underwent wedge excision only, and 2 required lobectomy. Careful roentgenographic evaluation was carried out in all patients in an attempt to avoid unnecessary thoracotomy. Goodwin and Snell's [12] concept that histoplasmomas continue to elaborate collagen at the periphery of the nodule appears valid since several of these patients that were followed preoperatively had enlarging nodules that were histoplasmomas. None of these patients, however, demonstrated concentric calcium laminations [16]. The 17 patients who were followed have shown no evidence of further pulmonary histoplasmosis, nodular or cavitary.

The patients with mediastinal histoplasmosis had signs and symptoms of disease at an earlier age than the pulmonary group. Ten of the 11 patients in this group were less than 30 years old, and all 4 of the patients explored for mediastinal mass lesions without fibrosis were less than 10 years old. These 4 patients are all asymptomatic at follow-up to four years. Mediastinal lesions, either in an encapsulated mass or noncalcified nodes, require tissue diagnosis whether or not they initiate symptoms [7]. In this small group of patients with granulomatous nonfibrosing mediastinal histoplasmosis, all patients were seen initially with pneumonia or bronchitis or both. Although no patient received postoperative antifungal therapy, 3 of the 4 were asymptomatic from excisional biopsy and the fourth was cured following middle lobectomy.

The single death in this series of 61 patients occurred in the group with fibrous mediastinitis. Five of the 7 patients in this group underwent resectional procedures, and 2 were biopsied only. Obviously, exuberant mediastinal fibrous proliferation represents a malignant reaction to histoplasmosis that occurs in a small percentage of patients with mediastinal granulomas. This either can occur as an immunological reaction to fungal antigen that is released when granulomas rupture or demonstrates the inability of the host to cease collagen formation around a central focus of infection. No specific time can be predicted when this might occur or which individuals are more likely to have mediastinal fibrosis secondary to histoplasmosis. Four of the 7 patients were less than 20 years old and the patient who died was a 57-year-old man who had had a left extrapleural pneumonectomy for recurrent pneumonia and necrosis secondary to mediastinal fibrosis. Although involvement of the superior vena cava developed in only 1 of our patients, this is probably a more common occurrence than our series demonstrates. Since the sequelae of mediastinal fibrosis may be severe, total excisional biopsies of undiagnosed mediastinal granulomas should be undertaken if technically feasible, with the aim of diminishing the likelihood of fibrosis developing. The role of amphotericin B in granulomas and fibrosis has yet to be determined; only 1 of our 11 patients received it postoperatively, and there was no documented therapeutic effect. It may be as Williams and Burford [20] suggested and Zajtchuk and colleagues [21] reiterated that an aggressive operative approach to mediastinal granulomas may prevent severe sequelae of fibrosis.

Interestingly, two cases in this series demonstrated *Histoplasma capsulatum* pericarditis. Although this is a rare cause of pericarditis with approximately forty cases described in the literature, it is one that occurs more frequently than thought and carries a good prognosis [14]. Both of our patients were acutely ill with febrile illness and large pericardial effusions necessitating drainage. Following pericardial window procedures, both improved dramatically. The pathogenesis of this granulomatous fibrinopurulent pericarditis is thought to be related either to direct extension from mediastinal nodes or pulmonary foci of histoplasmosis, or a hypersensitivity phenomenon. One of our patients demonstrated *Histoplasma capsulatum* in the hilar nodes as well as the pericardium, which lends credence to the direct extension theory. Follow-up in this group is only one year, and there is no evidence of constriction or calcification, which also confirms the findings of Picardi and colleagues that this type of pericarditis may carry a good prognosis [14]. Since the pericarditis was not a manifestation of disseminated disease nor were the conditions recurrent, amphotericin probably has little effect on the eventual outcome.

Although fungal endocarditis is rare, 1 patient in our series with long-standing aortic regurgitation required valve replacement for valvulitis secondary to disseminated histoplasmosis. Previous papers have supported the concept of secondary infection by *Histoplasma capsulatum* of a diseased valve, and our patient represents one of the earliest published accounts of valve replacement for histoplasma endocarditis [1, 2, 18, 19]. Because of his disseminated process, he was treated aggressively with 2 gm of amphotericin B preoperatively and received 2 additional gm postoperatively. His valve demonstrated *Histoplasma* organisms and showed the classic large vegetations of fungal endocarditis [17]. Although a rare cause of endocarditis, histoplasmosis must be considered an etiological agent in patients with signs of fungal endocarditis. All of these patients require aggressive antifungal treatment, and some may require valve replacement to improve valve function, remove a source of emboli, and excise lesions of low curability with drugs alone [17].

In summary, symptomatic histoplasmosis often is seen as a thoracic diagnostic and therapeutic problem. The natural history of pulmonary histoplasmosis is clear, and the aggressive nature of mediastinal histoplasmosis is becoming apparent. With more awareness on the part of surgeons, pericardial and cardiac disease caused by histoplasmosis will be more frequently recognized and treated. Finally, therapy with amphotericin B is indicated in cardiac histoplasmosis as well as cavitary pulmonary disease. The place of antifungal therapy in mediastinal and pericardial disease, although individualized, needs further data for definitive clarification.

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Carcinoid Heart Disease: Eight-Year Survival Following Tricuspid Valve Replacement and Pulmonary Valvotomy

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ABSTRACT **A 34-year-old man with carcinoid heart disease underwent tricuspid valve replacement and pulmonary valvotomy with enlargement of the right ventricular outflow tract in October, 1972. He has no cardiac symptoms eight years after operation. Only four previous successful valve replacements in patients with this condition have been reported.**

The carcinoid syndrome is seen, in most instances, in patients with malignant carcinoid tumor of the small bowel and hepatic metastases, though other primary sites may produce the syndrome [6, 9]. It results primarily from the release of large amounts of 5-hydroxytryptamine into the circulation from the metastases. As well as the striking hormonal effects of flushing, diarrhea, and bronchoconstriction, a typical fibrosis of the cardiac valves and endocardium develops in many of these patients. This usually involves the right side of the heart, although left-sided lesions have been described with bronchial carcinoids [5, 8].

Even though intractable congestive heart failure, subsequent to valve lesions, is thought to be a common cause of death in these patients [8], reports of surgical intervention are sparse. We have been able to find only four previous reports of successful tricuspid valve replacement in patients with this disease [1–4], and our patient appears to be the longest survivor at eight years after operation.

A 34-year-old man was referred for investigation in September, 1972. He had been completely well until five years previously when he noted the onset of attacks of flushing, lasting only a few seconds, but observed by many people to be very vivid. At first he had no effort intolerance, but after some months noted the onset of dyspnea on exertion. It gradually progressed until he was unable to walk any distance or play with his children. A diuretic was begun at that time and brought marked symptomatic improvement. The patient was referred for further investigation.

He gave no past history of cardiac disease, did not smoke, and had a moderate alcohol intake. He denied having any peripheral edema or orthopnea. He had noted diarrhea with episodes of flushing on some occasions.

Physical examination showed him to be quite plethoric. Blood pressure was 110/70 mm Hg and pulse was 90 beats per minute in sinus rhythm. Jugular venous pressure was elevated 6 cm above the clavicle (at 45 degrees). There was no peripheral edema or central cyanosis. The apex beat was difficult to localize, but a marked right ventricular heave was present. No precordial thrills were palpable. On auscultation, a grade 3/4 ejection systolic murmur was audible, maximal in the third and fourth left intercostal spaces. The second sound was normal with no increase in the pulmonic second sound. No diastolic murmur was audible.

The lungs were clear to auscultation. The liver was enlarged 6 cm and was hard, not tender, and nonpulsatile. There was no splenomegaly or other masses palpable. There were no ascites. The diagnosis was carcinoid syndrome, and the patient was admitted to hospital for further investigation.

Various laboratory studies were done. In the urine, 24-hour 5-hydroxyindoleacetic acid (5-HIAA) was extremely elevated at 4,445 μmole a day (normal, up to 32 μmole a day). Urine culture showed no growth. A liver scan revealed multiple areas of decreased uptake throughout the right lobe, and a liver biopsy confirmed the presence of metastatic carcinoid

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Table 1. Laboratory Data

Hematology	
Hemoglobin	16.9 gm/100 ml
White cells	5,600/mm^3
ESR	2mm/hr
Biochemistry	
Sodium	145 mEq/L
Potassium	4 mEq/L
BUN	13 mg/100 ml
Creatinine	1.2 mg/100 ml
Liver function	
Total protein	7 gm/100 ml
Albumin	4.4 gm/100 ml
Bilirubin	1.8 mg/100 ml
Alkaline phosphatase	50 U/100 ml
LDH	350 U/100 ml
SGOT	15 U/100 ml

ESR = erythrocyte sedimentation rate; BUN = blood urea nitrogen; LDH = lactic dehydrogenase; SGOT = serum glutamic oxaloacetic transaminase.

Table 2. Cardiac Catheterization Data

Variable	Measurement
Brachial artery (mm Hg)	136/90 $\overline{110}$
Right atrium (mm Hg)	
a	18
v	27 $\overline{14}$
y	5
Right ventricle (mm Hg)	65/0–7
Pulmonary artery (mm Hg)	15/7–9
Pulmonary artery wedge (mm Mg)	$\overline{4}$
Cardiac index (L/min/m^2)	2.3
Cardiac output (L/min)	4.2
Stroke volume (ml)	40
Pulmonary resistance (dyne sec cm^{-5})	95

tumor. Hematology and biochemistry results were normal apart from marginal elevation of bilirubin at 1.8 mg per 100 ml (normal, less than 1 mg per 100 ml) and lactic dehydrogenase at 350 U per 100 ml (normal, 150 to 300 U per 100 ml) (Table 1). Electrocardiogram showed sinus rhythm with an axis of +120 degrees and complete right bundle-branch block. Chest roentgenogram revealed a normal cardiac silhouette and clear lung fields. A small bowel series demonstrated no abnormality in the small intestine or stomach.

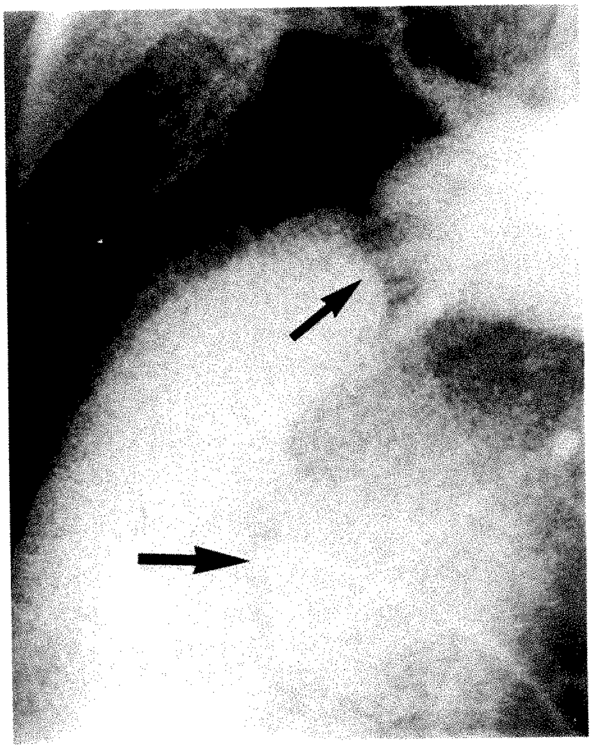

Fig 1. Right ventriculogram showing thickening of tricuspid and pulmonary valves (arrows).

The diagnosis of carcinoid syndrome having been established, cardiac catheterization was performed on October 5, 1972 (Table 2). This showed tricuspid and pulmonary valve stenosis, with a peak systolic gradient from the right ventricle to pulmonary artery of 50 mm Hg and from the right atrium to ventricle, in diastole, of 11 mm Hg. The pulmonary artery wedge pressure was 4 mm Hg and pulmonary vascular resistance, 95 dyne sec cm^{-5}.

Cineangiography showed the right ventricular outline to be smooth with normal trabeculation. The tricuspid and pulmonary valves were seen to be thickened (Fig 1).

Operative Findings

Operation was performed on October 26, 1972. The right atrium was tense and thickened. The tricuspid valve showed thickening of the cusps and stenosis with an orifice 1 cm in diameter. The pulmonary valve also was found to be thickened, the pulmonary valve ring itself being quite small.

A median sternotomy incision was used, and total cardiopulmonary bypass was established

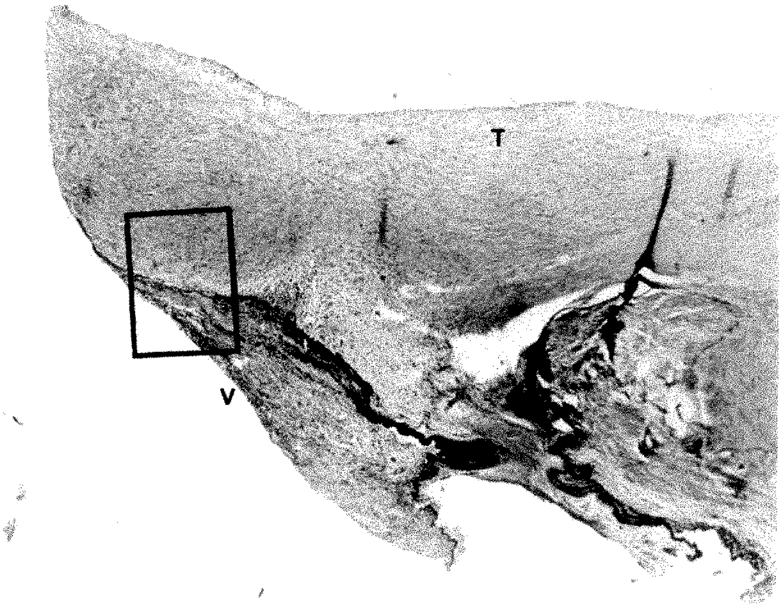

Fig 2. Section of a cusp of the pulmonary valve showing obvious thickening on its endocardial surface. (V = *valve cusp;* T = *thickening.) (Taenzer-Unna orcein stain;* ×22.5.)

in the normal manner. The pulmonary commissures were opened, and the valve was partially excised. The arteriotomy was then extended down into the right ventricular outflow tract and a gusset of pericardium sewn in to enlarge the pulmonary orifice. The tricuspid valve then was excised and replaced with a Starr-Edwards low-profile caged-disc mitral prosthesis (3M model 6500). This valve was selected because the right ventricular cavity was thought to be too small to accept a caged-ball prosthesis.

Bypass was withdrawn without any difficulty and after the patient's condition had stabilized, pressures were measured. The right ventricle to pulmonary artery systolic gradient was 10 mm Hg, and there was no diastolic gradient across the tricuspid valve. The patient's postoperative course was uneventful, and he was discharged two weeks postoperatively on a regimen of furosemide, 80 mg in the morning and 40 mg at night, potassium supplement, and phenindione, 20 mg twice a day.

Histological examination of the valve tissue showed gross thickening of the endocardium. It lacked elastic tissue and had the reticular pattern characteristic of carcinoid syndrome (Figs 2, 3).

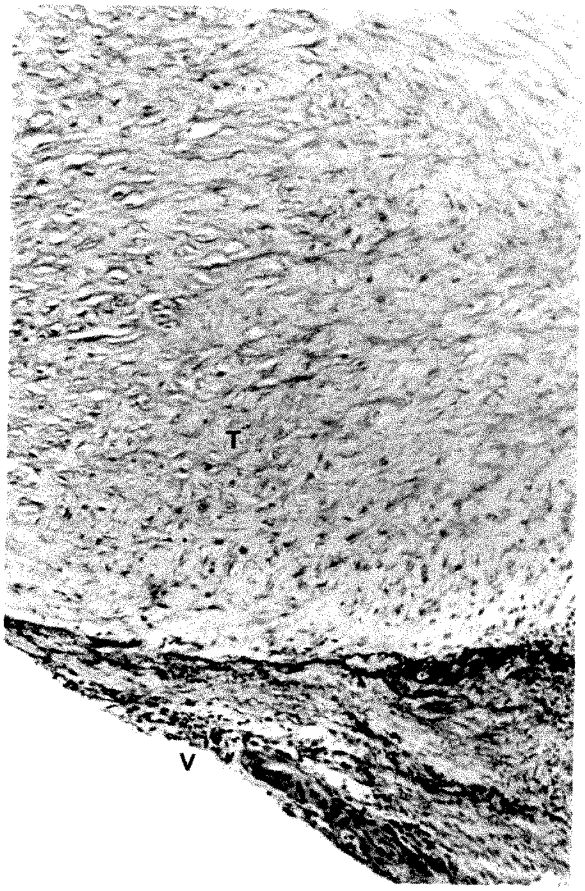

Fig 3. Higher power of marked area in Figure 2 demonstrating elastin-free collagenous thickening. (Taenzer-Unna orcein stain for elastin; ×*90 before 5% reduction.)*

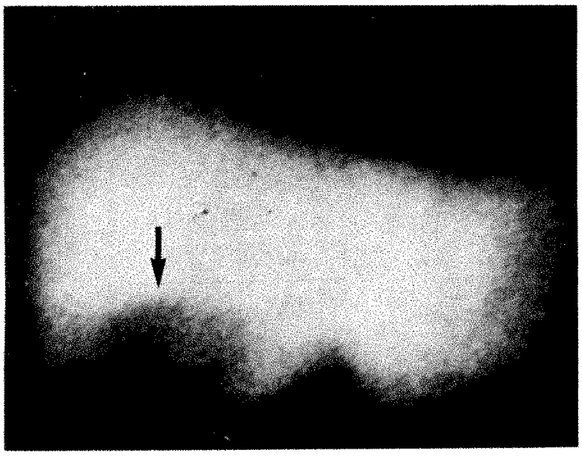

Fig 4. Liver scan done in July, 1978, shows a defect in the right lobe (arrow).

Follow-up

In the eight years since operation, the patient has remained free from cardiac symptoms. He does not consider himself limited in any way by the valve prosthesis and is able to work in the garden, play golf, and carry on his employment with no trouble. Chest roentgenogram remains normal and electrocardiogram is unchanged. His current medications are furosemide, 40 mg, and digoxin, 0.25 mg in the morning, phenindione, 20 mg twice daily, and potassium supplements. On this regimen, he considers his life comparable to that of his peers.

A recent radionuclide liver scan showed little, if any, progression of the metastatic disease (Fig 4). Urinary 5-HIAA levels have been found to be still markedly elevated at 1,950 μmole a day. The patient still has flushing attacks, an average of one per week, but is not inconvenienced by them. He has no diarrhea or bronchospasm and has never had any abdominal symptoms or signs apart from hepatomegaly.

Comment

The carcinoid syndrome was characterized by Thorson and associates [9] in 1954. It has been reported that long-term survival with this tumor is not uncommon [8, 10] even when metastases are present. In the patient reported by Honey and Paneth [3], symptoms suggesting carcinoid syndrome had been present for thirty years prior to valve replacement and nineteen years prior to initial laparotomy. In his review of the literature, Thorson [8] found that in 56 patients dying of carcinoid disease, heart failure was a contributory cause in 27 and the major cause in 16. Trell and colleagues [10] also found cardiac lesions to be an important cause of death in their review of 11 patients with carcinoid heart disease.

An attempt to surgically repair the valve lesions of carcinoid heart disease was made by Wright and Mulder [11] in 1963. No prosthesis suitable for tricuspid replacement was available at that time, and the patient was left with substantial tricuspid incompetence and died in the immediate postoperative period.

Only four subsequent reports of tricuspid valve replacement in patients with carcinoid heart disease have appeared since then. The patient of Aroesty and colleagues [1] survived for six years before dying of hepatic failure. The patients of Carpena and co-workers [2] and Honey and Paneth [3] were well at the time of reporting some two years postoperatively. The patient described by Lund and associates [4] died of malignant cachexia some four months after operation, without any recurrence of cardiac failure. This patient also illustrates the important part that the valvular lesions of carcinoid heart disease can play in the course of the disease. The patient was unusual in that he was seen not because of the symptoms of carcinoid syndrome, but because of cardiac disease. At no time had he any abdominal signs or symptoms referable to an intestinal primary, though he must surely have had one. In view of this and his response to valve replacement, it was not thought necessary to perform a laparotomy and resection to reduce tumor mass, though this is recommended to control hormonal symptoms [7].

In view of the importance of cardiac lesions as a cause of death in carcinoid syndrome, and the potential for prolonged survival with this tumor, we believe that operation should be undertaken in patients with this disease when hemodynamically indicated. The type of tricuspid prosthesis selected is dictated by the size of the right ventricular cavity. Pulmonary stenosis should be treated by valvotomy and outflow tract enlargement if necessary. Consequent pulmonary incompetence is well tolerated when pulmonary vascular resistance is normal and no left-sided valvular lesions are present.

No satisfactory explanation has yet been found for the occurrence of endocardial fibrosis typical of carcinoid heart disease. The valves are thought to have been normal prior to onset of the syndrome. Till the mechanism of this fibrosis is clarified, use of a tissue replacement valve probably should be avoided as it seems possible that the same pathological changes could be induced in the prosthesis.

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Patch Enlargement of the Aortic and the Mitral Valve Rings with Aortic-Mitral Double-Valve Replacement

Samuel Manouguian, M.D., and Paul Gerhard Kirchhoff, M.D.

ABSTRACT **In 1 patient, patch enlargement of the aortic valve ring was accomplished by extending the aortic incision into the anterior mitral leaflet. The pericardial patch broke from the aortic leaflet of the mitral valve on the fourth postoperative day. The resultant acute mitral incompetence necessitated mitral valve replacement also. An aortic-mitral double-valve replacement with attendent enlargement of both the aortic and mitral valve rings ensued. To our knowledge, enlargement of the aortic and mitral valve rings with aortic-mitral double-valve replacement has not been described in the literature.**

My colleagues and I have described elsewhere a new surgical procedure of radical enlargement of the aortic valve ring and left ventricular outflow tract by incising the aortic annulus, the aortic leaflet of the mitral valve, and the superior aspect of the left atrium [2–5, 8]. Following reconstruction of the resulting defects, the aortic valve was replaced with a suitable, larger prosthesis (Fig 1). In addition to enlarging the aortic root, application of this technique yields an enlargement of the mitral valve ring at the origin of the aortic leaflet of the mitral valve. To replace the mitral valve is not a primary goal of this technique.

In 1 patient who underwent patch enlargement of the aortic root, the pericardial patch was torn out of the aortic leaflet of the mitral valve on the fourth postoperative day. The resultant critical mitral insufficiency necessitated mitral valve replacement. By this circumstance, an aortic-mitral double-valve replacement with patch enlargement of both the aortic and mitral valve rings was performed. To the best of our knowledge, no report of an aortic-mitral double-valve replacement with patch enlargement of the aortic and mitral valve rings has been made in the literature.

In March, 1969, at the Department of Thoracic and Cardiovascular Surgery, Göttingen, a commissurotomy was performed on a 9-year-old patient with severe aortic valve stenosis. The aortic valve ring was narrow. Heart catheterization in February, 1972, done at the division of pediatric cardiology, Göttingen, revealed an aortic valve gradient of 115 mm Hg and a left ventricular pressure of 215/0 mm Hg. Cineangiography of the left ventricle displayed a very severe valvular aortic stenosis with extremely thickened, irregularly bounded valve leaflets (Fig 2). The unfavorable anatomical findings as well as the narrow aortic valve ring (about 15 mm in diameter) led to the decision to replace the aortic valve and to enlarge the aortic valve ring, done January 10, 1977.

Myocardial protection was carried out by infusion cardioplegia (Bretschneider's solution [1]). The aortic incision was extended for 2 cm into the aortic leaflet of the mitral valve, and the attachment of the left atrial wall at the base of the aorta was divided. The incision in the left atrial wall at the aortic root was then extended cranially to increase surgical accessibility. A fusiform pericardial patch was sutured to the V-shaped defect in the anterior mitral leaflet and in the aortic root with running suture lines. The resulting enlargement of the aortic annulus for about 25 mm allowed the implantation of a Björk-Shiley No. 23 aortic valve prosthesis.

The defect between the left atrial wall and the pericardial patch was closed with continuous suture, which also fixed the sewing ring of the aortic prosthesis. Occlusion of the left coronary

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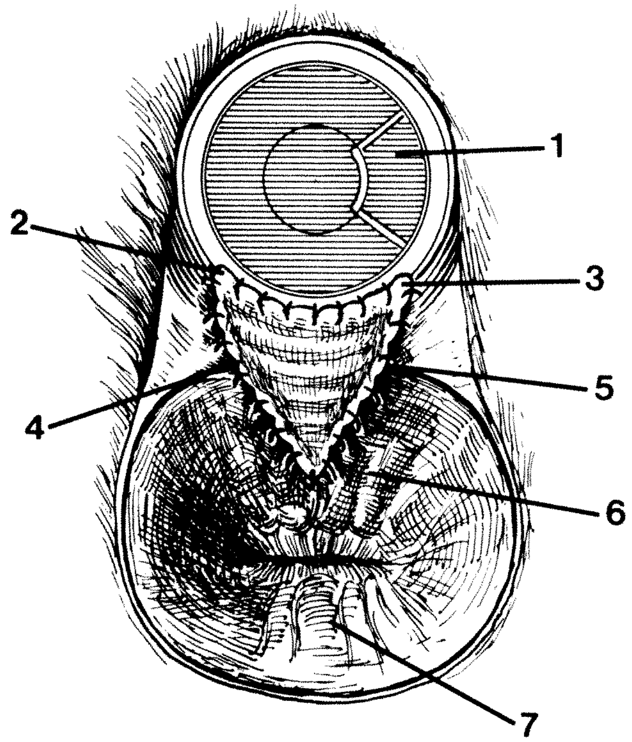

Fig 1. Enlargement of the aortic valve ring following patch plasty of the aortic leaflet of the mitral valve and the aortic base. In addition to enlargement of the aortic root (2, 3), enlargement of the mitral valve is shown (4, 5). The anatomical relationships are demonstrated semischematically as seen from the left atrium following resection of the left atrial wall. For clarity, the anatomical angle between the aortic root and mitral ostium is not shown. (1 = aortic valve prosthesis; 6 = anterior mitral leaflet; 7 = posterior mitral leaflet.)

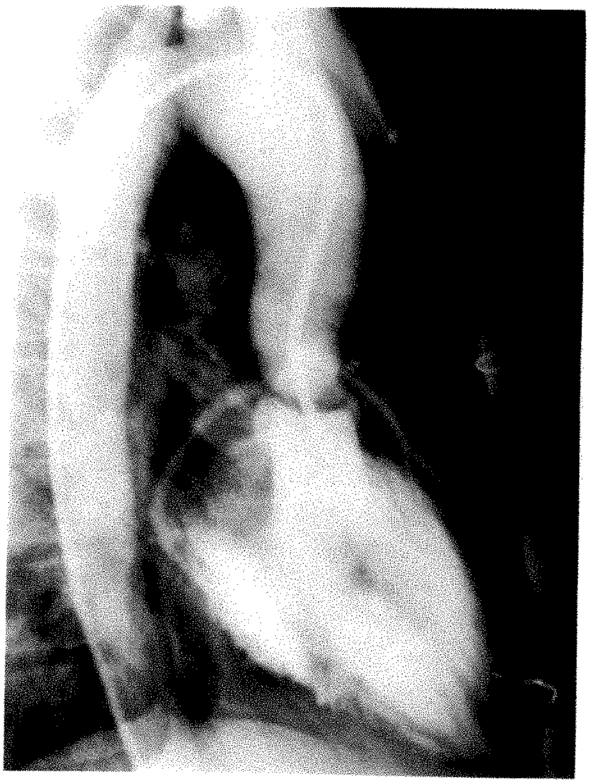

Fig 2. Levogram made after commissurotomy. It reveals valvular aortic stenosis with strongly thickened, irregularly bounded valve leaflets and a narrow valve ring.

ostium by the valve prosthesis made it necessary to cut out the latter. In doing this, the pericardial patch was damaged, necessitating its removal as well. Following a new pericardial patch plasty of the aortic leaflet of the mitral valve, the aortic valve was replaced with a No. 23 Björk-Shiley prosthesis.

Circulation was stable after removal of the heart-lung machine. Intraoperative pressure measurement in the left atrium gave no indication of mitral insufficiency. The patient's further course was uneventful, and there were no clinical signs of mitral incompetence. The occurrence of severe acute mitral insufficiency on the fourth day after operation (pulmonary capillary pressure was in excess of 40 mm Hg) necessitated immediate reoperation.

Myocardial protection was achieved with intermittent coronary perfusion and local myocardial cooling. Opening of the left atrium confirmed the suspicion that the pericardial patch, which had been stitched into the aortic leaflet of the mitral valve, had been ripped from its mooring. In the center of the leaflet was a triangular opening that looked as though it had been stamped out of the leaflet tissue (Fig 3). Its base was situated at the base of the aorta. The decision was made to replace the mitral valve rather than to provide a new patch plasty of the anterior mitral leaflet. The pericardial patch was trimmed at the base of the triangle, and the mitral valve was excised, and replaced with a No. 27 Björk-Shiley prosthesis with a supravalvular ring. In the area of enlargement of the mitral valve ring at the origin of the anterior mitral leaflet, the sutures were made at the base of the shortened pericardial patch and at the sewing ring of the aortic valve prosthesis (Fig 4).

In this manner, an aortic-mitral double-valve replacement with attendant enlargement of the aortic and mitral valve rings was accomplished.

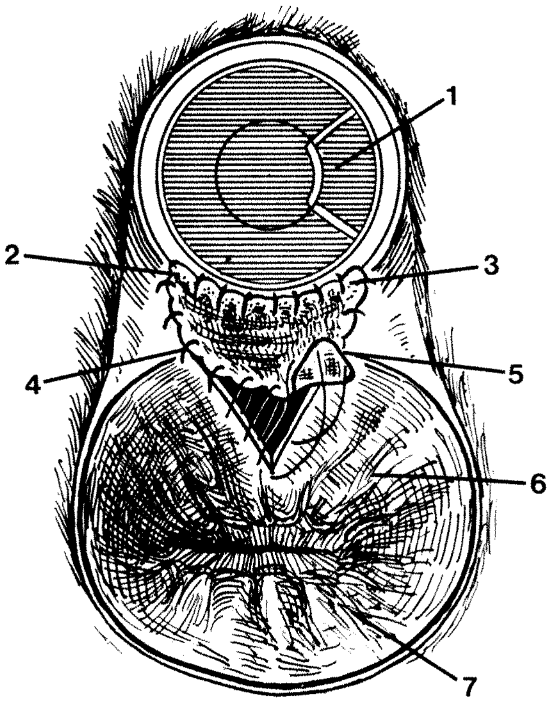

Fig 3. The tearing out of the pericardial patch sewn into the aortic leaflet of the mitral valve. A triangular opening is stamped out in the middle of the leaflet; its base lies on the aortic base. The anatomical relationships are shown semischematically as seen from the left atrium after resection of the wall of the left atrium. For clarity, the anatomical angle between the aortic root and mitral ostium is not shown. The enlargement of both the aortic valve ring (2, 3) *and the mitral valve ring* (4, 5) *is readily seen.* (1 = *aortic valve prosthesis;* 6 = *anterior mitral leaflet;* 7 = *posterior mitral leaflet.*)

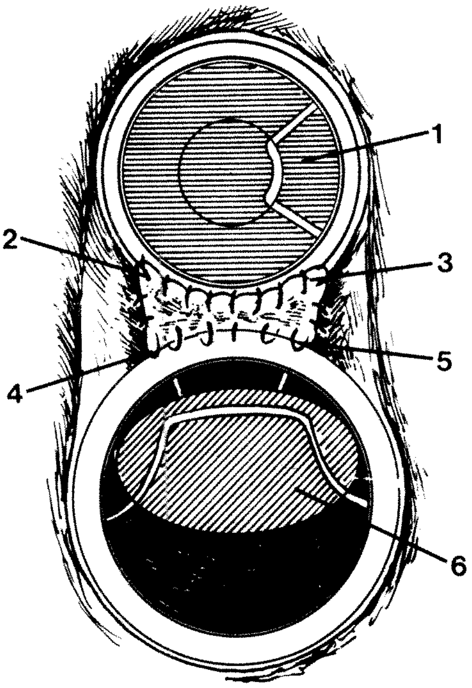

Fig 4. Mitral valve replacement after enlargement of the aortic valve ring as described in this study. The anatomical conditions are seen from the left atrium after excision of the left atrial wall. In the area of enlargement of the mitral valve ring at the origin of the anterior mitral leaflet, sutures are made at the base of the shortened pericardial patch and at the sewing ring of the aortic valve prosthesis. To make this diagram clearer, the anatomical angle between the aortic root and the mitral ostium is not shown. The enlargement of the aortic (2, 3) *and mitral* (4, 5) *valve rings is visible.* (1 = *aortic valve prosthesis;* 6 = *mitral valve prosthesis.*)

Figure 5 shows the topographical relations of the aortic and mitral valve prostheses to each other. With respect to cardiovascular status, the further course of the patient was remarkably favorable, despite complications introduced by pneumonia, atelectasis of the right lower lobe, and otitis media. The patient left the hospital on February 19, 1977, in good general condition.

The patient was examined in the division of pediatric cardiology of the Georg-August-University, Göttingen, in April and October, 1977, and March and December, 1978. He was in good clinical condition. A roentgenogram revealed no evidence of heart enlargement (cardiothoracic ratio = 0.48). The lungs appeared normal. The electrocardiogram showed some minor signs of left hypertrophy. There were no excitation recovery troubles. The function of the prosthesis was normal. Digitalis therapy was discontinued.

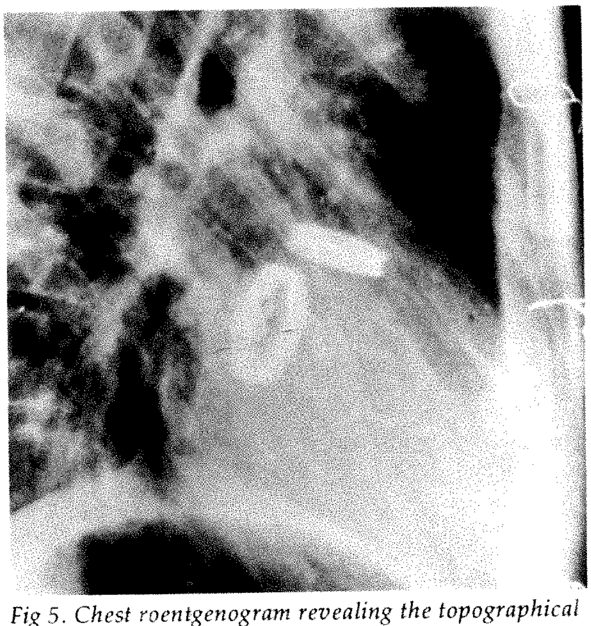

Fig 5. Chest roentgenogram revealing the topographical relations of the aortic and mitral valve prostheses to each other following aortic-mitral double-valve replacement. There is enlargement of the aortic and mitral valve rings.

Comment

Tearing loose of the patch stitched into the aortic leaflet of the mitral valve is a possible complication of the surgical technique of patch enlargement of the aortic valve ring by extending the aortic incision into the anterior mitral leaflet as described by one of us (S. M.). Between November, 1975, and April, 1979, 16 patients underwent this procedure. The complication occurred in 1 [8] and probably was precipitated by the fact that the pericardial patch had to be removed and restitched. This case report demonstrates the technical possibility of enlarging both aortic and mitral valve rings with aortic-mitral double-valve replacement.

The operative technique of enlargement of the aortic and mitral valve rings with aortic-mitral double-valve replacement was developed experimentally by one of us (S. M.) in 1976 and 1977 at the Department of Thoracic and Cardiovascular Surgery, Georg-August-University, Göttingen. The surgical technique as well as the results of the experimental work have been reported [7] and published elsewhere [6].

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Transaortic Cannulation for Balloon Pumping in a "Crowded Aorta"

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ABSTRACT **A technique for cannulating the ascending aorta or aortic arch to introduce a balloon catheter for intraortic balloon pumping is described. It is performed without the use of a partial occlusion clamp. This technique is useful when multiple anastomoses in the ascending aorta leave no room for the application of a vascular clamp. Three patients in whom this technique was used are reported.**

Balloon counterpulsation is sometimes needed at the end of cardiopulmonary bypass. Transfemoral insertion of the balloon may not be possible due to atherosclerotic obstruction of the iliac arteries. Transaortic insertion of the balloon through the ascending aorta has been used in these instances [5–9]. A partial occlusion clamp is applied to the anterior wall of the aorta. The aortic wall is incised, and a woven fabric graft is anastomosed end-to-side to the entire aortic wall [3, 4, 6]. In rare situations, it is impossible to apply the clamp because of lack of space in the ascending aorta. A very short aorta, multiple saphenous vein anastomosis, the aortotomy suture line of an aortic valve replacement, or the aortic perfusion cannula are reasons for the absence of free space. In these situations, we have found useful the technique to be described.

Surgical Technique

The area of the aorta chosen for introduction of the balloon is stripped of adventitial tissue. A woven Dacron graft 12 mm in diameter is sutured to the aortic wall. The anastomosis is performed with a continuous suture of double armed 4-0 polypropylene. The bites do not penetrate the full thickness of the aortic wall. A No. 15 scalpel blade is introduced in the lumen of the graft, and a full-thickness puncture of the aortic wall is made at the center of the anastomosis. The scalpel is removed, and bleeding is controlled with a vascular clamp applied to the graft.

A 6 mm Hegar dilator is introduced inside the graft, and the aortic incision is dilated. As the dilator is removed, the clamp is reapplied to the graft. The anastomosis between the aorta and the graft is checked for bleeding points. A skin incision is made over the second right intercostal space, and the free end of the graft is drawn through it. Then the counterpulsation balloon is introduced through the graft into the aorta and advanced to the desired position in the descending aorta. Bleeding between the graft and the balloon cable is controlled in the routine manner (Figure).

The insertion of the balloon can be done at any place in the ascending aorta or the left lateral inferior wall of the aortic arch. For insertion in the latter position, the pericardial reflection between the aorta and the pulmonary artery is divided; blunt dissection frees the aortic arch from mediastinal tissue. The rest of the procedure proceeds as already described.

Comments

Complications following transfemoral insertion of the intraaortic balloon are relatively frequent. Infections, ischemia of the legs, aortic dissection, bowel gangrene, and death related to the balloon have been described [1]. Although prophylactic insertion of an intraaortic balloon before open-heart operation has been advocated, not everybody agrees with the indications for such a measure [2]. In most patients who need counterpulsation during cardiac operations, the balloon can be inserted through the femoral artery. In some, however, a transthoracic insertion is obligatory because of the presence of peripheral atherosclerosis.

In some patients with a short aorta, aortic

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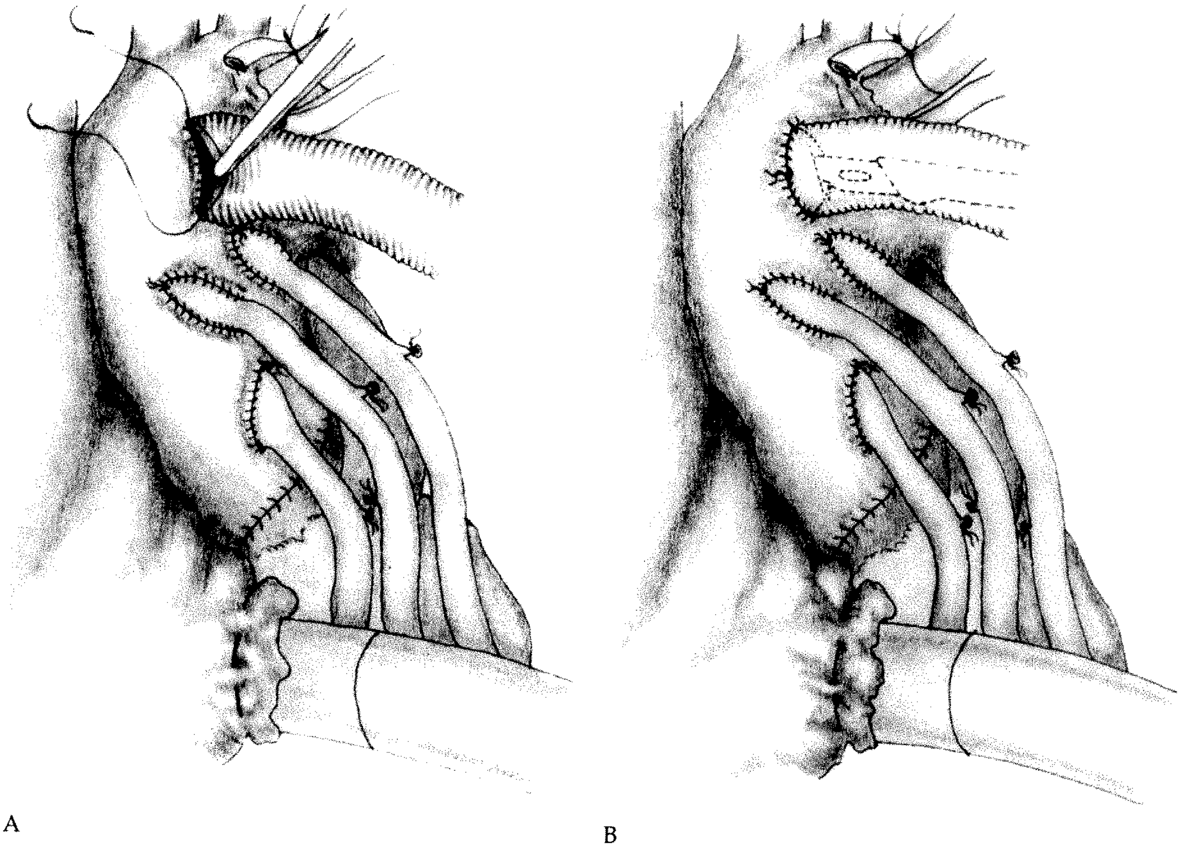

(A) Anastomosis between the aorta and graft is performed by taking bites only through adventitial and elastic tissue. Care should be taken not to pierce the intima of the aorta. (B) Insertion of the scalpel through the graft and the stab incision in the walls of the aorta.

valve replacement, and multiple aortosaphenous vein anastomoses, there is no room to apply a partial occlusion clamp to the ascending aorta. We have seen 3 such patients in the last three years and used the technique described here. These patients had aortic valve replacement and triple aortocoronary bypass with the saphenous vein. They could not be weaned from bypass at the end of the procedure. Transfemoral insertion of the balloon was impossible, and there was no room to apply a partial occlusion clamp. The balloon was inserted using our technique. In 2 patients the graft was anastomosed just to the right of the aortic cannula and in the third, through the left lateral wall of the aortic arch. The 3 patients were weaned from cardiopulmonary bypass. Two patients died of ventricular arrhythmias 8 and 13 hours after operation. In the third patient, the balloon was removed 48 hours later. The patient is alive and well four months after operation.

Although we have used this technique only in these 3 difficult patients, it can be used in any patient needing transthoracic aortic cannulation. No complications related to the technique have been encountered in our patients.

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An Improved Retractor for Cardiac and Thoracic Operations

M. T. McEnany, M.D.

ABSTRACT **Several standard abdominal wall retractors have been modified to improve exposure at the extremes of thoracic and groin incisions and to enhance the efficiency and comfort of the assistant in supplying adequate visibility in these areas.**

In the performance of cardiac and thoracic surgical operations and their ancillary components, retraction at the limits of the sterilely draped field is often necessary. In procedures requiring simultaneous surgical activity in the chest and groin, the primacy of the thoracic procedure frequently precludes easily satisfactory exposure in the inguinal area. Full exposure of the cervical end of a sternotomy incision can be hampered by the patient's chin and by the metal and cloth draping devices at the head of the operating table.

To improve the facility with which the neck, the high femoral area, and the posterior end of thoracotomy incisions can be exposed with the least amount of distraction to the anesthesiologist and other team members, and the least amount of discomfort to the assistant, several frequently used abdominal wall retractors have been modified. The modifications make these retractors more useful in the cramped quarters encountered in cardiac and thoracic operations because they do not require that the instrument be pulled parallel to the patient's

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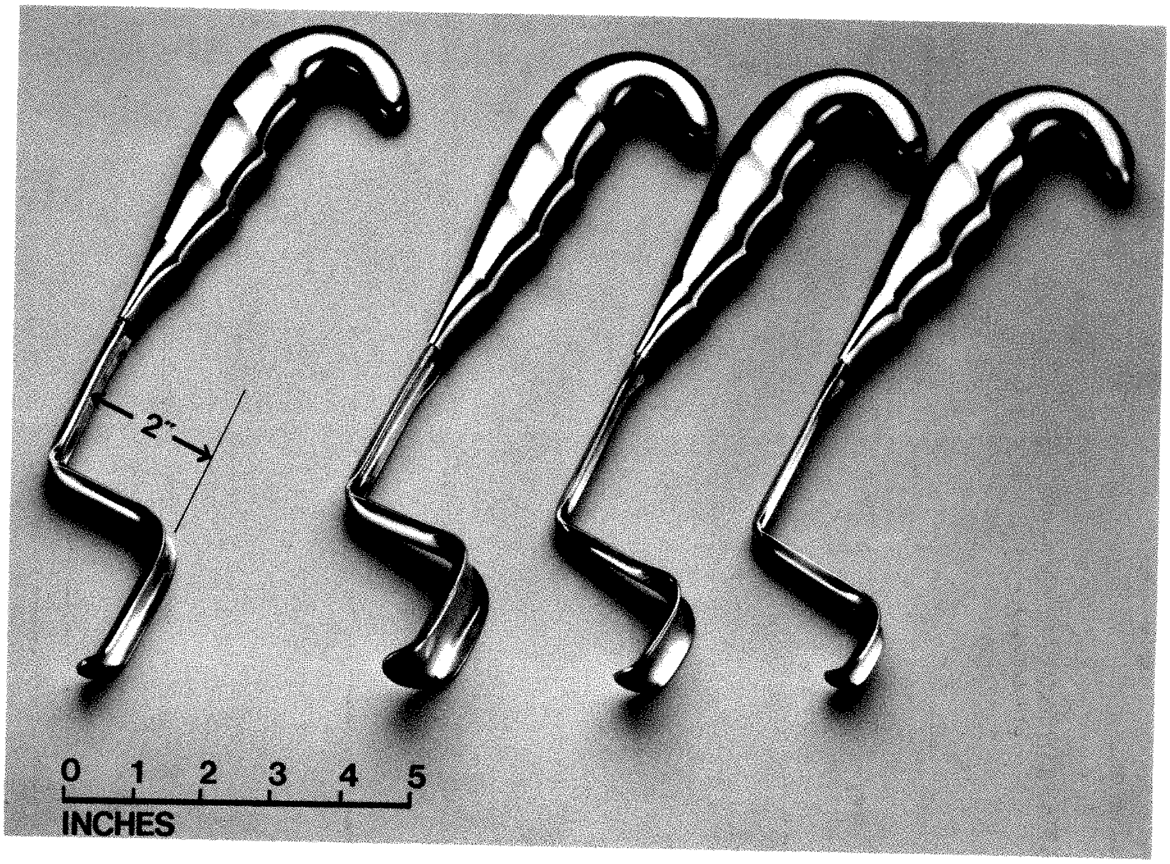
Retractors with blades of different dimensions.



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body. This allows easy fitting of the retractor into the limited space at the end of the incision. Excellent exposure can be obtained by modest effort of the forearm and wrist.

Several standard abdominal wall retractors were modified by bending the shaft of the retractor to a right angle, two inches (5.08 cm) from the blade. Retractors with blades measuring 1 × 1½ inches, ¾ × 1 inch, 1½ × 2 inches, and ¾ × 2 inches (Figure) have been found to be especially useful in the locations mentioned and are commercially available.* The comfort experienced by the surgical assistant and the excellent exposure afforded recommend these retractors for more general use.

---

*The Miriam Hospital, Department of Surgery, Providence, RI.

Scatter Radiation to the Hands from Insertion of Transvenous Pacemakers

Joseph G. Antkowiak, M.D.

ABSTRACT **Using ring film-badge dosimeters, scatter radiation to the hands of the operating surgeon was measured during the transvenous insertion of nine permanent pacemakers and one inferior vena cava umbrella. Average fluoroscopy time was 12 minutes. The average dose of radiation was 25.5 mrems. The calculated yearly exposure of a surgeon inserting pacemakers at this rate is approximately 3 R. This falls well within the "maximum permissible dose" to the hands, which is currently 75 R per year.**

Wholey [4] recorded higher radiation exposure to the hands during angiography when the procedure was done through the brachial artery rather than the femoral artery. He related this directly to the proximity of the tube source to the operator's hands. Thus a surgeon using the cephalic or jugular vein for surgical procedures under fluoroscopy would be expected to receive even larger doses of scatter radiation to the hands.

Methods

A commercial ring film-badge dosimeter* was worn beneath a sterile glove on the second finger of the operating surgeon. Lead aprons were worn, of course, by all members of the operating team to protect against total-body irradiation. Total-body irradiation for each individual procedure was not a part of this study. Between December 23, 1978, and January 29, 1979, ten consecutive procedures (insertion of permanent pacemakers and one inferior vena cava (IVC) umbrella) were done using a C-arm fluoroscope.† The cephalic vein was used to insert transvenous electrodes and the internal jugular vein for the IVC umbrella.

Results and Comment

Results are shown in the Table. Radiation exposure ranged from less than 10 mrems (minimal) to 80 mrems. The largest dose (80 mrems) was recorded during a less than average fluoroscopy time, probably because there was difficulty passing the transvenous electrode beyond the subclavian vein. Considerable manipulation was required with the x-ray tube close to the operator's hand. Conversely, although 39 minutes of fluoroscopy time were needed to position another electrode, only 40 mrems of radiation was recorded. The difficulty here was in placing the electrode in the right ventricle, at a greater distance from the operator's hands.

Since these procedures were done during a period of thirty-seven days, the calculated yearly dose of scatter radiation to the hands of a surgeon working at this rate would be roughly 3 R. This falls well within the "maximum permissible dose" to hands, which is 75 R per year

Radiation Exposure Study: December 23, 1978, to January 29, 1979

Transvenous Insertion	Fluoroscopy Time (min)	Exposure (mrem)
Pacemaker	5½	50
Pacemaker	39	40
IVC umbrella	14	M
Pacemaker	7	M
Pacemaker	8	30
Pacemaker	6½	80
Pacemaker	5	M
Pacemaker	7	M
Pacemaker	24	30
Pacemaker	3¾	M
Total	119¾	255
Average	12	25.5

IVC = inferior vena cava; M = minimal, i.e., less than 10 mrem (an average of 5 mrem was used in totaling).

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Accepted Oct 5, 1979.

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†"Siremobile 2U," Siemens, 186 Wood Ave South, Iselin, NJ 08830.

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[3]. In spite of these encouraging data, it would seem prudent to keep radiation exposure to a minimum since harmful effects of low-dose radiation are difficult to evaluate [2]. Using the fluoroscope intermittently and shutters to reduce the field size will decrease the radiation field and exposure to all operating-room personnel. With special equipment for coronary arteriography, Begg and Hans [1] reported much lower doses to the hands (2.8 mrems) per single procedure (average fluoroscopy time, 8.42 minutes).

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CORRESPONDENCE

Certification and Recertification

To the Editor:

Certification by the American Board of Thoracic Surgery (ABTS) clearly signifies that a qualified applicant has adequately absorbed current concepts in thoracic surgery. There is no evidence, however, that any similar test can measure the qualifications or success rate of thoracic surgeons ten years in practice. One might even anticipate that an intelligent, competent surgeon would be better informed on many matters common to his own particular practice than most university-based Board Examiners, and that an answer preferred on theoretical grounds might be at variance with practical experience. In other words, certification and recertification are seemingly such unrelated issues that one can seriously question any push for recertification requirements, especially by those currently involved in the certification process.

The recent ABTS article [1] (accorded editorial status in our own *Annals of Thoracic Surgery*) was signed by fifteen co-authors. Not surprisingly, these fifteen ABTS members also belong to The Society of Thoracic Surgeons (STS), the only inclusive organization of qualified thoracic surgeons. One can, therefore, disregard the ABTS claim that it remains "free from bias and impartial" [1] (perhaps even unprejudiced) *only because* ABTS members are appointed from five different organizations. The latter fact supposedly and, we are told, fortunately makes the ABTS an independent bureaucracy.

If such an independent bureaucracy truly existed, it would be another sad example of the medical profession's rush to "do it to ourselves before *they* do it to us" (in this case by creation of the very "outside forces legislating a standard" [1] that the ABTS was originated to prevent). The major ongoing charades of "Democracy in the STS" and "Independence of the ABTS" simply cover self-perpetuation of the "Old-Boy Network" of thoracic surgeons. In general, our leaders are well-respected men in their field, but they obviously need guidance or replacement when their unsupported personal opinions become regulations that will harass thoracic surgeons many years after present ABTS members have retired.

A prime example of the need for the STS to more closely control our ABTS subset is the present ABTS requirement for *mandatory recertification* of all diplomates certified after 1975. This stringent new demand for ongoing recertification examination is not applicable to older STS members now ruling the ABTS, who are thereby placed in an unwarranted position of privilege. Any arbitrary new standard developed only for others suggests conflict of interest, an ongoing desire to dominate young surgeons who escaped "The Dictatorship of the Program Director" when they entered private practice.

The majority of thoracic surgeons in practice are members of the STS. The majority of STS members are thoracic surgeons in practice, *not* "Program Directors," although the STS leadership continues to be closely held and rotated among "Program Directors." As a first step toward fulfilling their formal STS and ABTS obligations to thoracic surgeons in practice, our fifteen "Program Directors" on the ABTS (who not coincidentally are also prominent STS leaders) might respond to the following questions:

1. What specific advantages accrue to thoracic surgeons or the public by having the ABTS maintain its facade of independence from the STS?
2. Conversely, what serious damages could be anticipated if the ABTS were to become openly responsive to the democratically expressed will of the annual assembly of the STS?
3. Has there been any attempt by the STS or ABTS to measure quality or appropriateness of thoracic surgical care now delivered by practicing thoracic surgeons?
4. What will be measured in the recertification process, how will it be done, and is there any information on whether this measurement process itself has any relationship to, or effect on, the quality of care thereafter delivered by the examinee?
5. Are there, in fact, *any* scientific data that show beneficial effects of recertification on the quality of medical care delivered in *any* medical field?
6. Is the push for recertification likely to have any effects other than perpetuation of the present pecking order in thoracic surgery ("Program Directors" over private practitioners), instigation of unnecessary litigation (doctor versus doctor, doctor versus hospital, doctor versus malpractice plaintiff), or interference with timely local delivery of thoracic surgical care (by those who may be eminently qualified for what they do but perhaps not for a meddlesome recertification examination on aspects of thoracic and cardiovascular surgery that they commonly refer elsewhere or do not even encounter, due to vagaries in their own practice pattern or referral structure).

The *mandatory* recertification process *remains an unproved remedy for an undefined problem* with great downslope potential for young thoracic surgeons. Any broad application of the recertification process is totally unjustified by currently available information. It might, however, be interesting to embark upon a pilot study of the medical competence of ABTS members and the STS leadership before and after their submission to a recertification examination.

Recent votes by STS members in Assembly (January, 1979) demonstrated that we vigorously oppose *mandatory* recertification. Why, therefore, do our ABTS/STS leaders still promote the recertification requirement, and why only for younger thoracic surgeons?

Arndt von Hippel, M.D.

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Reference

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Editor's Note

It is important that Dr. von Hippel's most recent letter be published before the STS meeting in January, 1981. It is not possible to meet that deadline and at the same time present a reasoned response from the Board to the many questions and misconceptions in his letter. Obviously, there will be further discussion of these problems at the STS meeting.

Herbert Sloan, M.D.

Mandatory Recertification

To the Editor:

At the recent annual meeting of The Society of Thoracic Surgeons, a debate concerning mandatory recertification of thoracic and cardiovascular surgeons occurred during the business session. The majority of the members present at that business session passed a motion opposing mandatory recertification, thereby defeating the intention of the executive committee of the Society, which was to obtain a vote in favor of mandatory recertification. At least one representative of those members opposed to recertification requested that the results of the vote be published in *The Annals of Thoracic Surgery.*

My understanding of our bylaws is that the members present at the business session, regardless of number, constitute a quorum. Therefore, the vote taken, which indicated that the majority of those present opposed mandatory recertification, was legally and parliamentarily correct. However, inasmuch as only approximately 15% of the total membership of the Society was present at the session, and inasmuch as the issue of recertification is of such extreme importance, I thought that a rebuttal to that vote was appropriate.

In retrospect, I think all would agree that the leaders of our Society could have been somewhat more democratic and indeed considerably more political in their method of bringing the concept of recertification to the Society for debate and vote. The feeling seemed to prevail, at least among the opponents of recertification, that the motion to approve recertification was the result of some clandestine arrangement. I must admit I think that such notions simply reflect the emotionality surrounding this issue.

Individualism, probably nowhere more personified than by the thoracic surgeon, produces an intense hostile reaction to the mere mention of the word *mandatory*. One can easily sympathize with thoracic and cardiovascular surgeons who are ten, twenty, and even thirty years out of their training, some of whom may not have ready access to academia and programs of continuing education, and many of whom have a wealth of clinical surgical experience, who are rather suddenly called upon to be reviewed and tested.

It is my view, however, that the practice of thoracic and cardiovascular surgery is at once the most challenging, most sophisticated, most rapidly advancing, and most physically and psychologically intrusive speciality. I do not care what lawyers or pilots or engineers demand of themselves. I do not subscribe to the notion that we should only reexamine ourselves when others reexamine themselves or force us to do so. It has always been the characteristic of leaders and champions that they voluntarily reexamine themselves in order to always be certain that they are maintaining the highest possible standards of performance. As a thoracic and cardiovascular surgeon I do not wish merely to support the concept of recertification, but rather to demand it for my speciality.

I believe that The Society of Thoracic Surgeons will discuss recertification again at its next annual meeting. In the meantime, I suggest that regional or state committees representing the totality of the membership be established to study the philosophy and mechanics of recertification. It is my belief that when this democratic process is accomplished and when the concept of recertification is discussed next year with all the facts at our disposal, the Society will go on record as being overwhelmingly in favor of recertification of its members.

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Loose Anvil on TA-30 Stapler

To the Editor:

Stapling instruments are employed in many pulmonary operations. Initial concern regarding security of the stapled bronchus has abated with greater experience. Although malfunction of the instrument is rare, we recently experienced a dramatic example. Since the event can be prevented, we are bringing it to the attention of readers of The Annals.

We have used the stapling instrument frequently during the past decade, and a short time ago noticed that the anvil was loose. It tended to slip out when the instrument was being passed behind the structure to be stapled. We thought this slipping was due to a bad lot of staples. Then we noted that the instrument seemed to fire correctly on the right upper lobe bronchus, but that the bronchus was not closed properly with the green staples and had to be sutured. Finally, during a right radical pneumonectomy, the white staples were fired into the right pulmonary artery, but when the instrument was unwound, the vessel was wide open. We have become so confident that no precautionary suture had been applied to this vessel. We plugged the vessel with a finger and were able to apply a curved Pott's clamp. The patient required 1,600 ml of blood during the suturing of the vessel. The patient had an uncomplicated postoperative course and was discharged home.

Examination of the cartridge showed that the plunger had compressed the staples properly, but, presumably because the loose anvil had tilted despite fixation by the pin, the staples were not lined up correctly with the depressions on the anvil. Therefore, they had not penetrated and closed through both walls of the vessel. A few had become attached to the pulmonary artery, and fear of tearing the artery made it difficult to withdraw the instrument from the pool of blood. Subsequent discussion with the manufacturers indicated that over the years sufficient wear had occurred in our TA-30 from the sharp steel anvils that the standard-sized staples no longer fitted. Since many surgeons have been using staplers in thoracic operations for many years, care should be taken to return the instrument to the manufacturer if the anvil seems loose.

Raymond C. Read, M.D.
John M. Ransom, M.D.

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Selective Bronchial Tamponade

To the Editor:

It is nothing new to those who have patients with bronchoesophageal fistula that management of the condition is very difficult. Despite all efforts, the pathological process oftentimes proves to be fatal because of flooding of the tracheobronchial tree by digestive tract secretions.

A patient of mine underwent esophagogastrectomy for megaesophagus secondary to Chagas' disease. A bronchoesophageal fistula developed late and led to severe respiratory failure due to flooding of the tracheobronchial tree. I was aware of the technique described by Swersky and co-workers (Ann Thorac Surg 27:262, 1979) by which selective bronchial tamponade is accomplished by means of a Fogarty balloon catheter inserted through a flexible fiberoptic bronchoscope to stop hemoptysis in patients with cystic fibrosis. It occurred to me that such a technique might prove useful in this patient. Indeed, with a No. 4 Fogarty catheter, tamponade of the segmental bronchus that gave access to the fistulous track was achieved and prevented further flooding of the patient's respiratory tract. The pulmonary condition was allowed to stabilize before a definitive surgical repair was undertaken.

Although not the definitive treatment, selective bronchial tamponade with a Fogarty catheter is simple, inexpensive, and easily attainable at bedside. Furthermore, it can buy important time until the patient's condition is stabilized to allow elective repair of the basic pathological condition.

José F. T. da Rosa, M.D.

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REVIEW OF RECENT BOOKS

Bethune (2nd ed)

By Roderick Stewart
Hamden, CT, Archon Books, 1979
210 pp, illustrated, $15.00

Reviewed by Lyman A. Brewer, III, M.D.

The name of Bethune is known to this generation of thoracic surgeons because of his efficient rib shears in use today. But should we know more about this contumacious idealist, who broke with conservative Canadian medical and Western democratic tradition and died for the people of communist China? In a painstakingly documented, three-year study involving interviews with more than 150 people in six countries, the author emphasizes that we should.

The story of Bethune is that of a brilliant, erratic, sometimes contradictory crusader who fought with tenacious determination for causes that were dear to him. When it was discovered that he had pulmonary tuberculosis, he went to Trudeau Sanitorium. This experience gave him an interest in thoracic surgery and a compassion for the poor, who in that era generally died of lack of antituberculosis treatment. Bethune believed that universal medical care provided by the state was the answer. His idealism drove him to Spain to support the Loyalists. However, on his return to Canada, June 14, 1937, to raise money for this cause, his increasingly leftist and finally pro-communist lectures provoked a storm of criticism and made it almost impossible for him to return to his former position in thoracic surgery.

The opportunity to serve with the communist forces in China in January, 1938, opened up a new way of life for Bethune. During the twenty-one months he was with the 8th Route Army, Bethune developed a network of mobile field hospitals, which were located close to the front lines and geared to guerilla warfare, and a practical training school for army surgeons, and compiled the textbook for this field medical school. It was in one of these forward mobile hospitals during an operation on a broken leg that the chisel Bethune was using sliced into the middle finger of his left hand. A virulent, apparently streptococcal infection developed. Without sulfa drugs, antibiotics, or proper care, the infection spread and in less than two weeks, on November 12, 1939, Bethune died of septicemia.

Roderick Stewart has captured the thrill and excitement that this arrogant and extraordinary man found in serving the peasants of China. He has demonstrated how Bethune's passionate commitment to the communist cause became an example for 800 million Chinese people to follow. With the current rapprochement between the United States and the People's Republic of China, the chronicle of this westerner fanatically devoted to an ideal (which he believed was the start of international peace) and, because of it, unmindful of the most appalling conditions under which he worked, becomes an important and truly fascinating story.

Loma Linda, CA

Trauma to the Heart and Great Vessels

By Panagiotis N. Symbas, M.D.
New York, Grune & Stratton, 1978
200 pp, illustrated, $24.50

Reviewed by J. Kent Trinkle, M.D.

This book is written by a surgeon who obviously is experienced in managing cardiovascular trauma. He did not merely compile information from the literature, but drew heavily on his experience and that of his colleagues. The book covers intrathoracic cardiovascular trauma in great detail and has an extensive bibliography. It is not suitable for an evening of "light reading," but is very valuable as a reference text or an intensive review of a specific problem. The numerous illustrations aid the reader's understanding of anatomy, pathophysiology, and operative technique.

I recommend that this book be included in medical libraries and used as a reference for trainees in thoracic surgery. It is less suitable for medical students or emergency room physicians who wish to acquire some general knowledge.

San Antonio, TX

INFORMATION FOR AUTHORS

Original manuscripts on thoracic, cardiac, and peripheral vascular surgery will be considered for publication in *The Annals of Thoracic Surgery* with the understanding that they be submitted only to this journal. Transfer of copyright to The Society of Thoracic Surgeons is a condition of publication; a form for this purpose appears elsewhere in the issue (see contents). Send manuscripts preferably by certified or registered mail to Herbert Sloan, M.D., Editor, *The Annals of Thoracic Surgery*, C-7079 University Hospital, Ann Arbor, MI 48109.

The Annals welcomes correspondence. Letters are reviewed according to the same standards as other contributions. Unsigned letters cannot be published.

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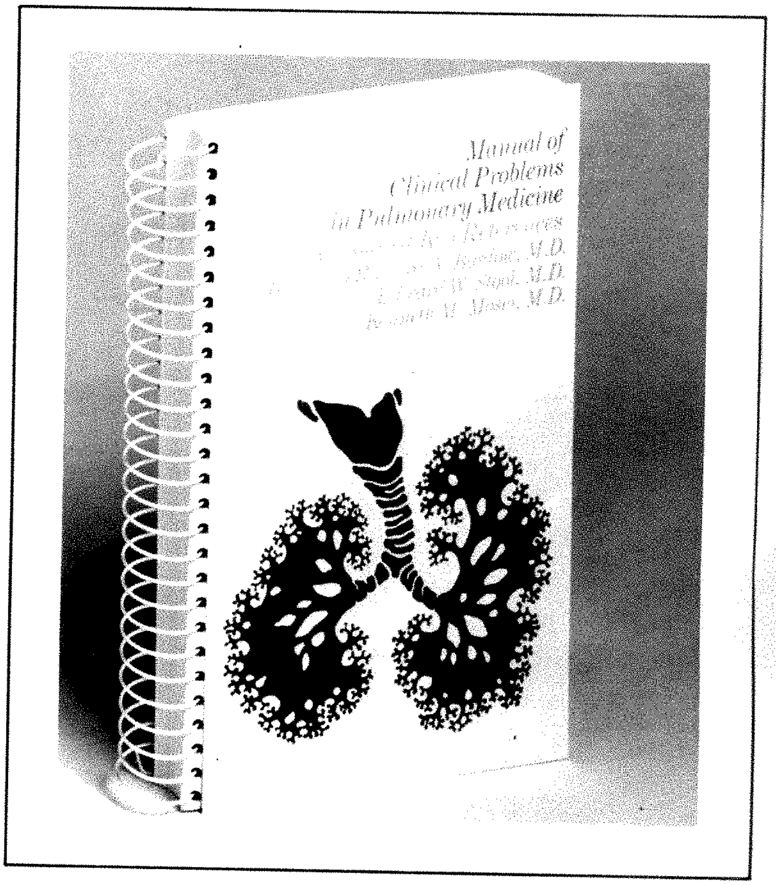

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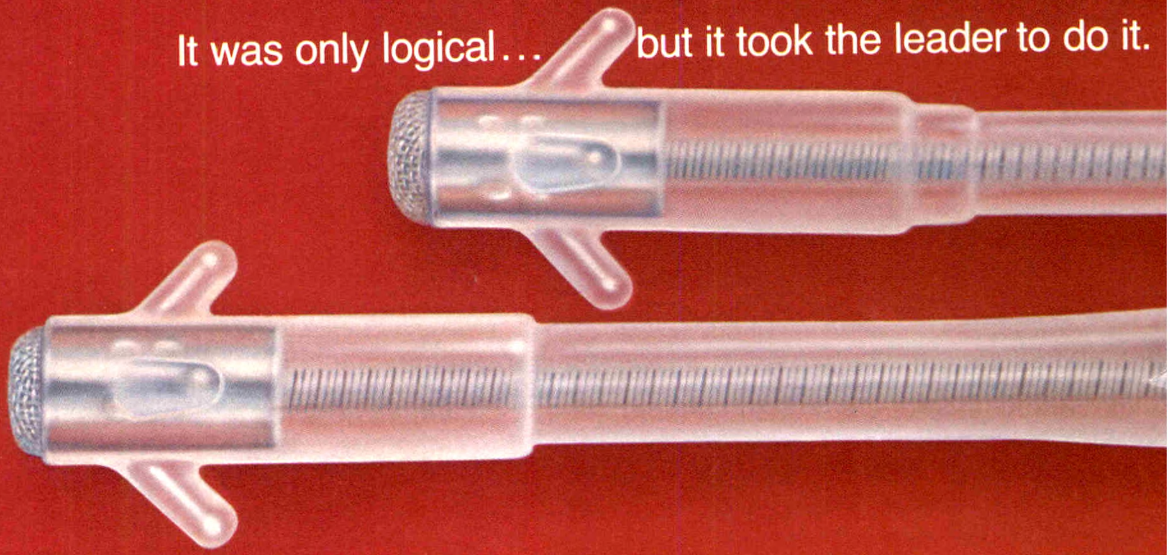

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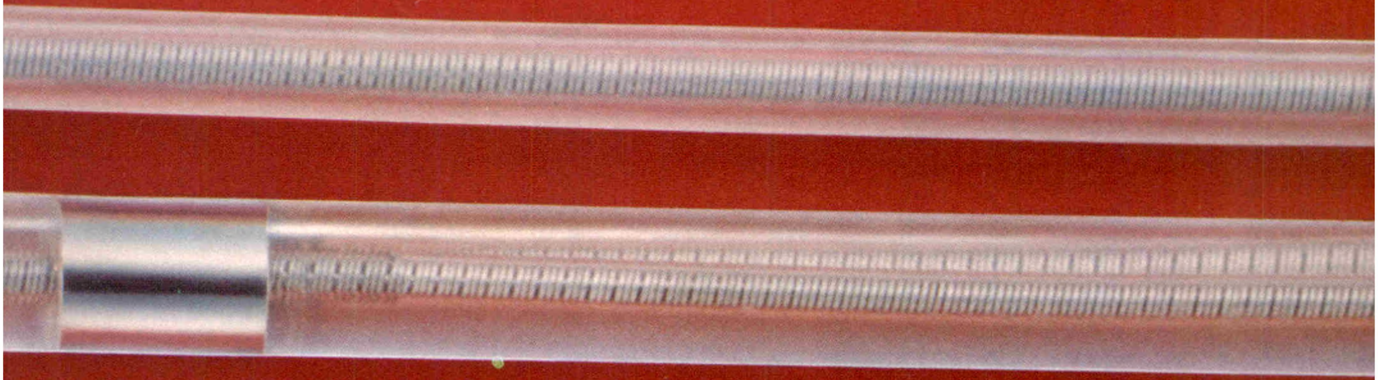

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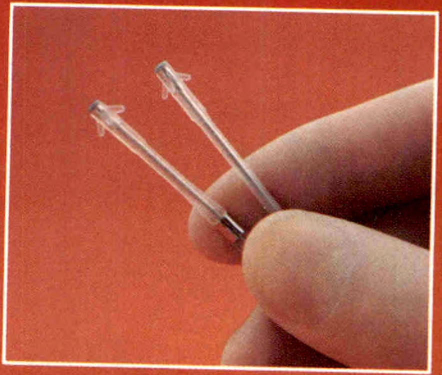

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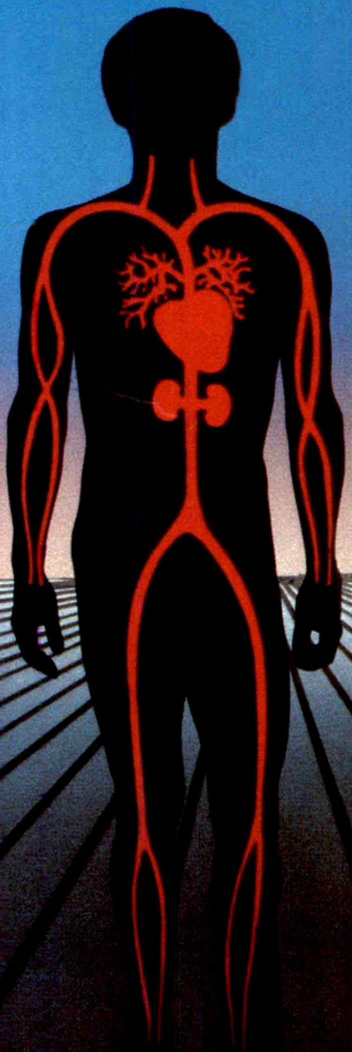

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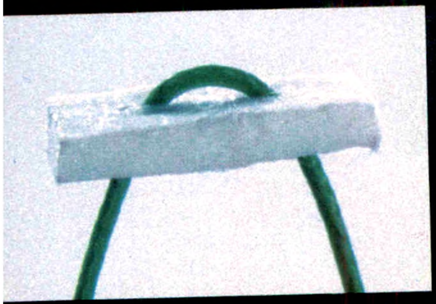

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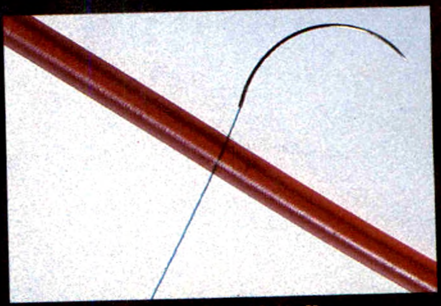

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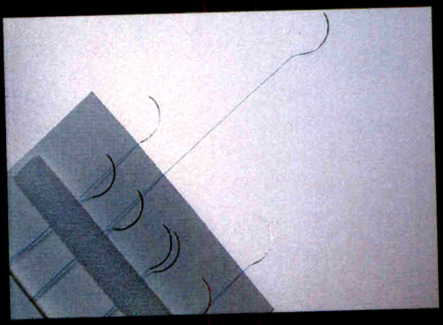

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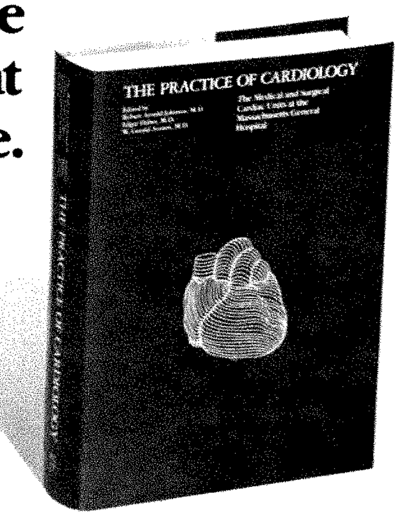

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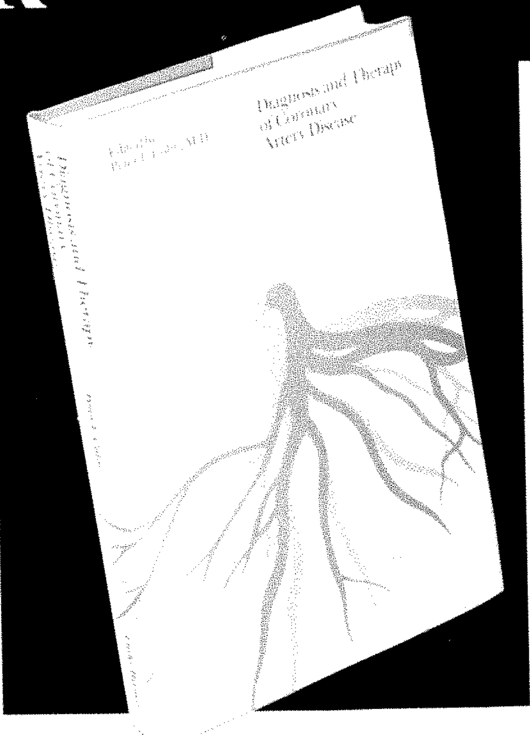

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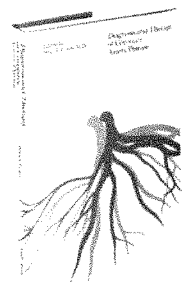

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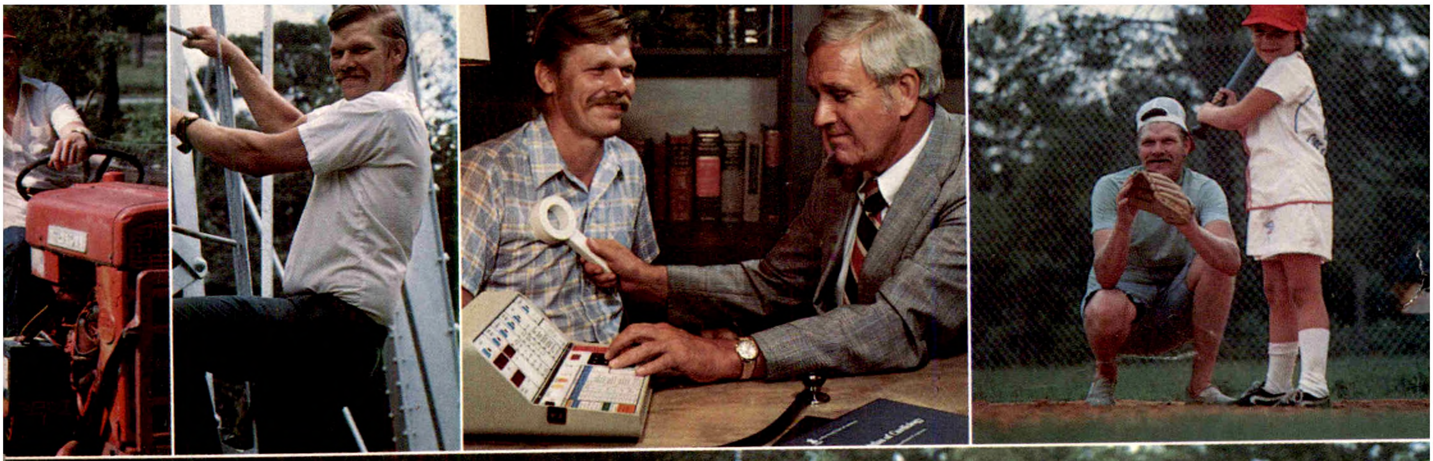
The first annual Primary Children's Medical Center Cardiac Surgery Symposium will be held at Prospector Square Ski and Conference Center, Park City, UT, February 18–20, 1981.

Principal topics to be discussed are Pulmonary Vascular Disease, Pharmacological and Mechanical Support of the Failing Ventricle, Congenital Valvular Obstructive Disease, and Technical Aspects of Cardiopulmonary Bypass in the Young Infant. The guest faculty includes Gerald Buckberg, M.D., Aldo Castanada, M.D., James Malm, M.D., Michael Nihill, M.D., Marlene Rabinovitch, M.D., and S. Subramanian, M.D.

Registration fee will be $250.00 except for guest speakers and residents who will be admitted free.

Applications can be obtained by writing to Edwin C. McGough, M.D., Program Chairman, Primary Children's Medical Center Cardiac Surgery Symposium, Primary Children's Medical Center, 320 12th Ave, Salt Lake City, UT 84103.

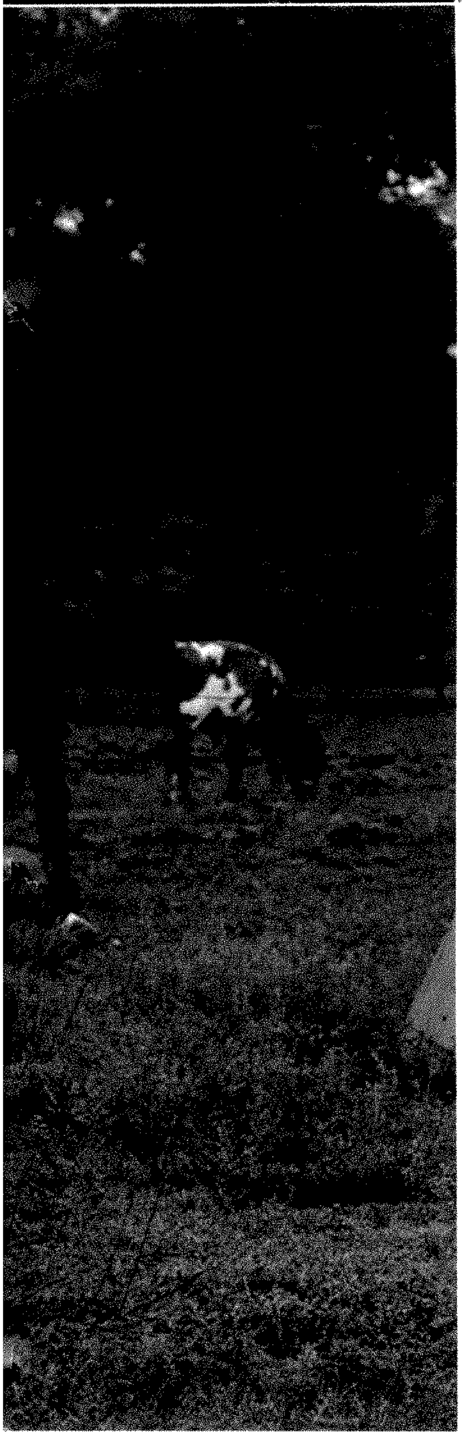


termedics Pulse Generators

DICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacemaking are increasing as pacekers become more sophisticated and as advanced methods for tient management become more widespread. Generally accepted dications for long-term cardiac pacing include but are not limited (1) sick sinus syndrome; (2) chronic, symptomatic drug-resistant sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting with intractable, recurrent, congestive heart failure; cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias who have been shown to benefit from temporary cardiac pacing are considered candidates for permanent cardiac pacemaking.

The indications for permanent pacing in the presence of acute myocardial infarction have not yet been rigorously defined. Fact to be considered include the location of the myocardial infarct, presence or absence of symptoms, ventricular rate, mechanism o the arrhythmias, and response to therapy. In general, symptoma drug-resistant bradyarrhythmias which impair cardiac output ar considered indications for pacing in patients with acute myocar infarction, regardless of infarct location.



A CyberLith® Pacemaker helped make these pictures of Wayne Sackett possible.

A LIFETIME OF MASSIVE HEART PROBLEMS IS BEING CONTROLLED WITH A CYBERLITH PACEMAKER, AN AORTIC VALVE, AND SELECTED DRUG THERAPY.

You'd never know by looking at him now, but ten years ago this man collapsed from disabling palpitations while mowing the lawn.

But thanks to an Intermedics CyberLith pacemaker, an aortic valve replacement, and continuing drug therapy, Wayne D. Sackett is more than just back on his feet. He's an active family man, a farmer, and Chief Plant Operator of the Water Department of Deland, Florida.

Taking care of an 11-acre farm is no small task, but Wayne and his wife enjoy making it a family affair with their three children. And the children know that when the chores are all done, it's time for play. Wayne has his favorites—softball, water skiing, fishing, and hunting—and the rest of the family likes to get in on the action.

For Wayne Sackett, as well as his family, the multi-programmable CyberLith pacemaker from Intermedics has proved to be more than a life-saver. In combination with the new valve and the drug therapy, it has been a life-enhancer. And because his physician has him telephonically monitored on a regular basis and can noninvasively make any changes necessary, chances are good that Wayne and his family can go on living as actively as they are now.

Wayne's CyberLith is just one model in the growing Intermedics family of thin, lightweight pacemakers that permit noninvasive programming of stimulating rate, pulse width, sensitivity level, and pacing mode. Because of the CyberLith's long history of reliability—longer thar any other programmable multi-parameter pacemaker line—Wayne will probably still be going strong when his five-year-old son is in college.

CyberLith. It could be the pacemaker of choice for your patients.

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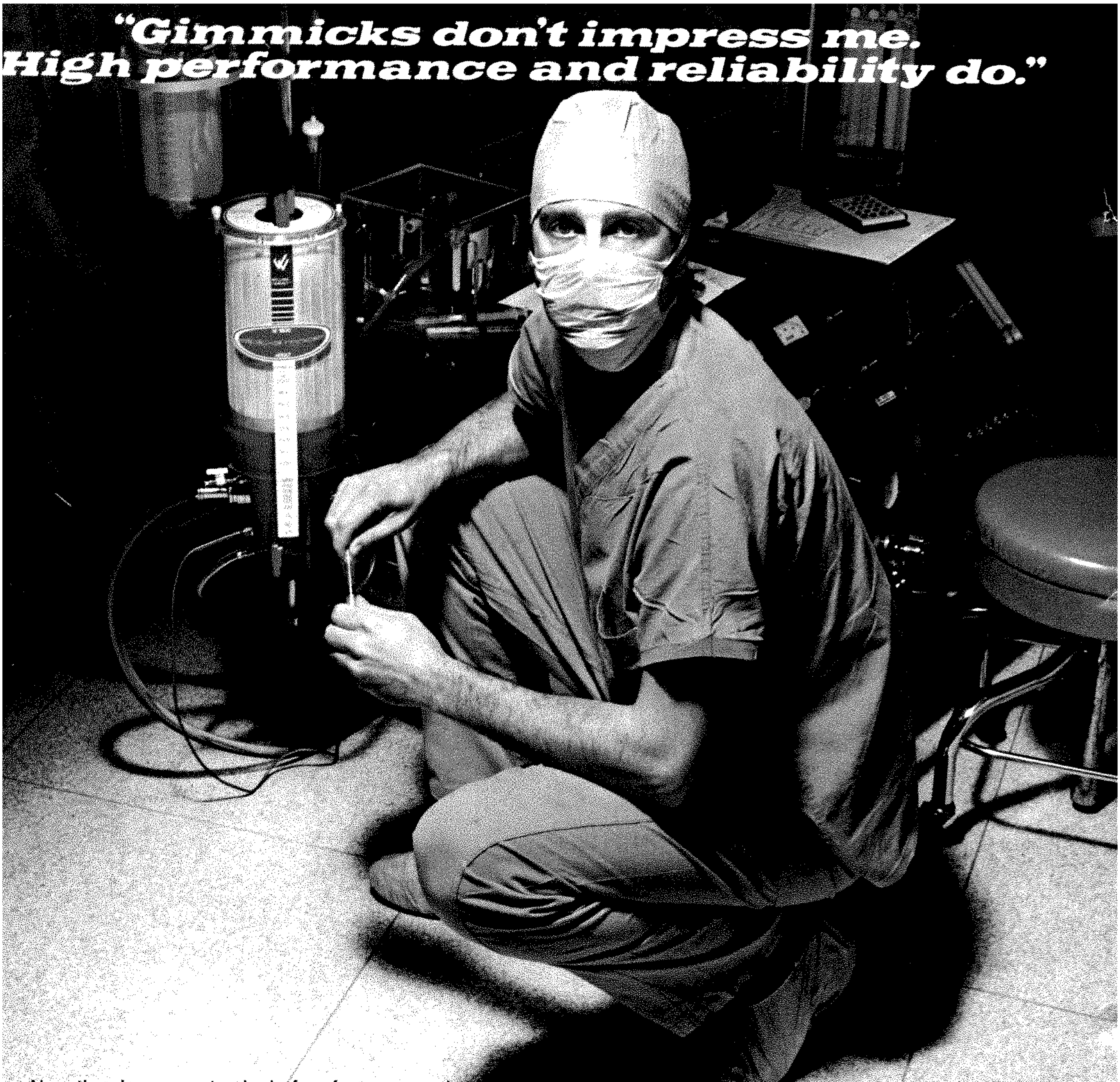
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THE ANNALS OF THORACIC SURGERY

Volume 30 Number 5 November 1980

Seventeenth Annual Meeting of
The Society of Thoracic Surgeons
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Extended in vitro activity* against gram-negative organisms†: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, P. rettgeri, P. morganii, P. vulgaris,*† *Enterobacter,*† and *Haemophilus influenzae.*[1,2]

Among newer cephalosporins, only Mandol has in vitro activity* against *H. influenzae* comparable to that of chloramphenicol and superior to that of ampicillin.[3]

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1 g (equivalent to cefamandole activity) in 10 and 100-ml-size vials.

Demonstrated increased in vitro activity* against *Enterobacter*† as compared with other cephalosporins.[4]

In vitro activity* against gram-positive organisms, including *Staphylococcus aureus, S. epidermidis,* beta-hemolytic and other streptococci,† and *Streptococcus pneumoniae.*

Mandol provides in vitro activity* against anaerobes.‡

Achieves therapeutic levels in pleural and joint fluids, in bile and bone.§

May be administered both I.M. and I.V.

*In vitro activity is not necessarily indicative of clinical effectiveness.

†*Pseudomonas, Acinetobacter calcoaceticus* (formerly *Mima and Herellea* species), most *Serratia,* enterococci (e.g., *S. faecalis*), and some strains of *P. vulgaris* are resistant in in vitro tests. Initially susceptible strains of *Enterobacter* may occasionally become resistant during therapy.

‡Most strains of *Bacteroides fragilis* are resistant in vitro; however, infections caused by susceptible strains have been treated successfully.

§Tissue analysis gives primarily qualitative rather than meaningful quantitative data as to the presence or absence of an antibiotic in a particular body fluid or tissue. Therapeutic efficacy cannot be predicted by the level attained in a specific body fluid or tissue.

Note: Mandol should be given cautiously to penicillin-sensitive patients and is contraindicated in patients with known allergy to cephalosporins.

References:

1. Antimicrob. Agents Chemother., 9:452, 1976.
2. Antimicrob. Agents Chemother., *8*:679, 1975.
3. Antimicrob. Agents Chemother., *8*:91, 1975.
4. Antimicrob. Agents Chemother., 9:994, 1976.

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Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Mandol is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, *Klebsiella* species, *Staphylococcus aureus* (penicillinase and non-penicillinase-producing), beta-hemolytic streptococci, and *Proteus mirabilis*

Urinary tract infections caused by *Escherichia coli*, *Proteus* species (both indole-negative and indole-positive), *Enterobacter* species, *Klebsiella* species, group D streptococci (*Note:* Most enterococci, e.g., *S. faecalis*, are resistant), and *S. epidermidis*

Peritonitis caused by *E. coli* and *Enterobacter* species

Septicemia caused by *E. coli*, *S. aureus* (penicillinase and non-penicillinase-producing), *S. pneumoniae*, *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae*, and *Klebsiella* species

Skin and skin-structure infections caused by *S. aureus* (penicillinase and non-penicillinase-producing), *S. pyogenes* (group A beta-hemolytic streptococci), *H. influenzae*, *E. coli*, *Enterobacter* species, and *P. mirabilis*

Bone and joint infections caused by *S. aureus* (penicillinase and non-penicillinase-producing)

Clinical microbiologic studies in nongonococcal pelvic inflammatory disease in females, lower respiratory infections, and skin infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Mandol has been used successfully in these infections in which several organisms have been isolated. Most strains of *Bacteroides fragilis* are resistant in vitro; however, infections caused by susceptible strains have been treated successfully.

Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefamandole. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, Mandol may be used concomitantly with an aminoglycoside (*see* Precautions). The recommended doses of both antibiotics may be given, depending on the severity of the infection and the patient's condition. The renal function of the patient should be carefully monitored, especially if higher dosages of the antibiotics are to be administered.

Antibiotic therapy of beta-hemolytic streptococcal infections should continue for at least ten days.

Contraindication: Mandol is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE THERAPY WITH MANDOL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

In newborn infants, accumulation of other cephalosporin-class antibiotics (with resulting prolongation of drug half-life) has been reported.

Precautions: Although Mandol rarely produces alteration in kidney function, evaluation of renal status is recommended, especially in seriously ill patients receiving maximum doses.

Prolonged use of Mandol may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly). There may be a false-positive test for proteinuria with acid and denaturization-precipitation tests.

As with other broad-spectrum antibiotics, hypoprothrombinemia, with or without bleeding, has been reported rarely, but it has been promptly reversed by administration of vitamin K. Such episodes usually have occurred in elderly, debilitated, or otherwise compromised patients with deficient stores of vitamin K. Treatment of such individuals with antibiotics possessing significant gram-negative and/or anaerobic activity is thought to alter the number and/or type of intestinal bacterial flora, with consequent reduction in synthesis of vitamin K. Prophylactic administration of vitamin K may be indicated in such patients, especially when intestinal sterilization and surgical procedures are performed.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Usage in Infancy—Mandol has been effectively used in this age group, but all laboratory parameters have not been extensively studied in infants between one and six months of age; safety of this product has not been established in prematures and infants under one month of age. Therefore, if Mandol is administered to infants, the physician should determine whether the potential benefits outweigh the possible risks involved.

Adverse Reactions: *Hypersensitivity*—Maculopapular rash, urticaria, eosinophilia, and drug fever have been reported. These reactions are more likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—Thrombocytopenia has been reported rarely. Neutropenia has been reported, especially in long courses of treatment. Some individuals have developed positive direct Coombs tests during treatment with the cephalosporin antibiotics.

Liver—Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been noted.

Kidney—Decreased creatinine clearance has been reported in patients with prior renal impairment. As with some other cephalosporins, transitory elevations of BUN have occasionally been observed with Mandol; their frequency increases in patients over 50 years of age. In some of these cases, there was also a mild increase in serum creatinine.

Local Reactions—Pain on intramuscular injection is infrequent. Thrombophlebitis occurs rarely.

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Volume 30 Number 5 November 1980

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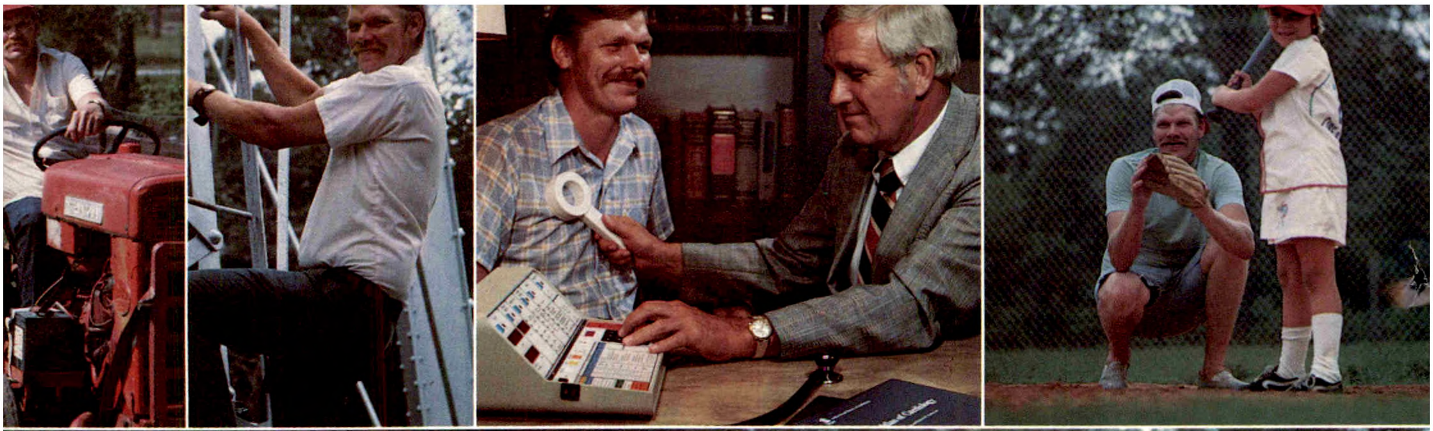

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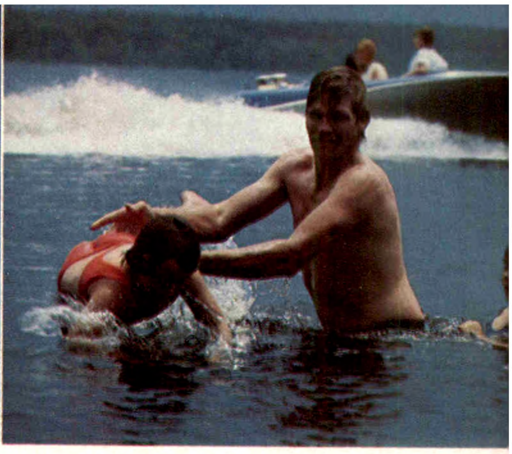

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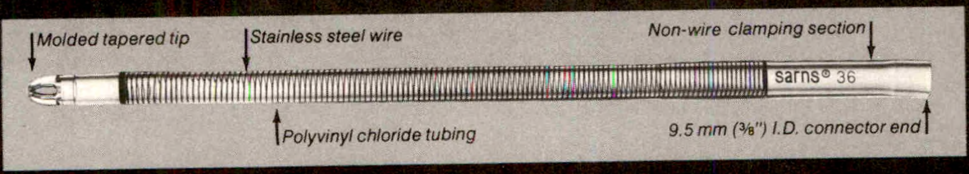
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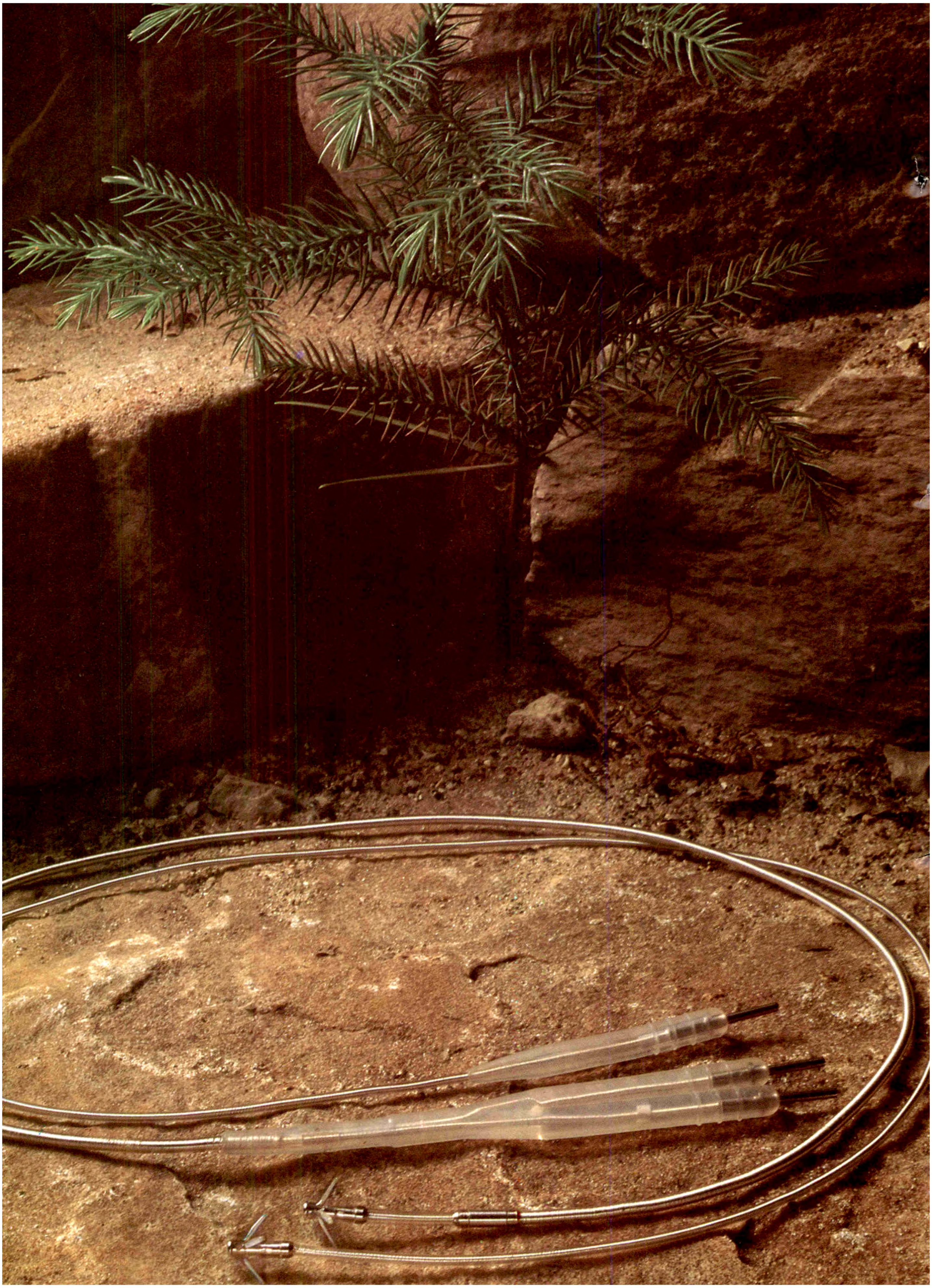

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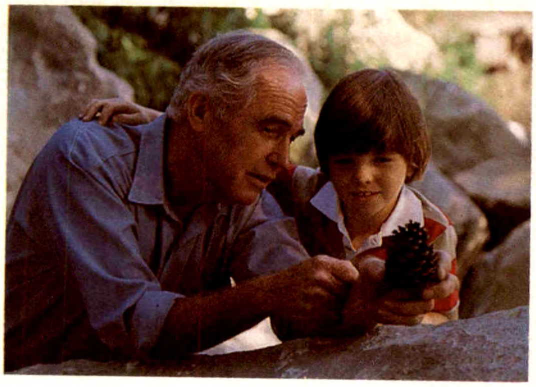

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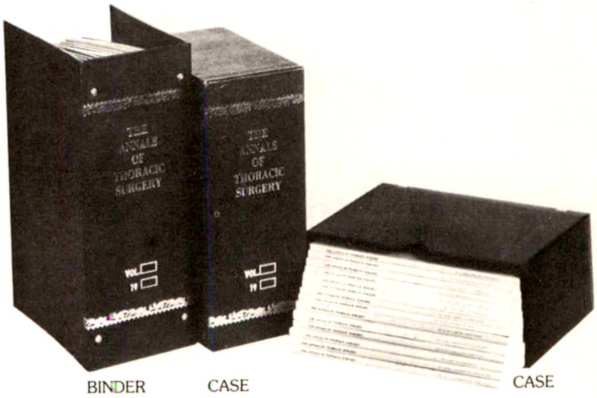
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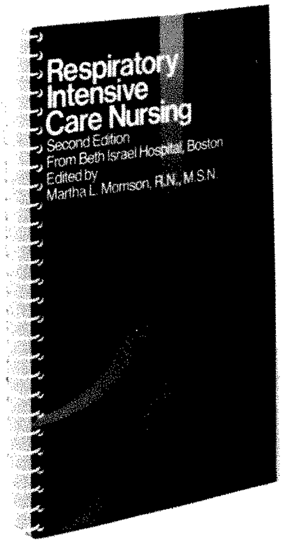

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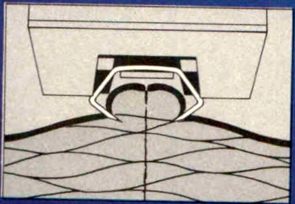

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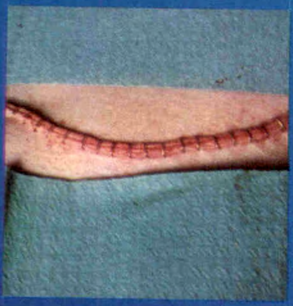

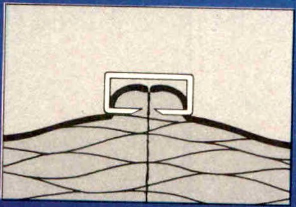

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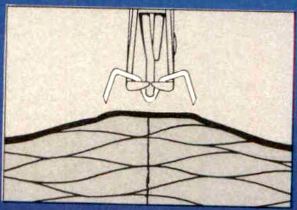

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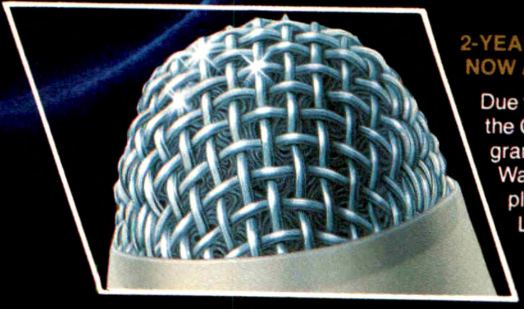

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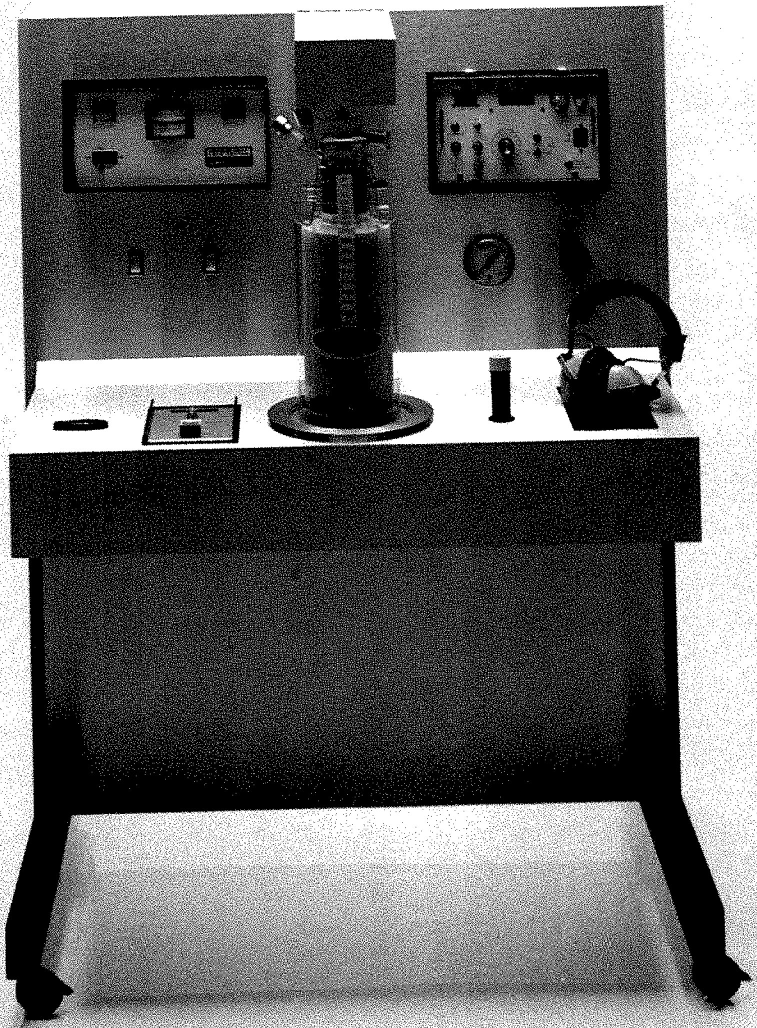

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Open Biopsy for Chronic Diffuse Infiltrative Lung Disease: Clinical, Roentgenographic, and Physiological Correlations in 502 Patients

Edward A. Gaensler, M.D., and Charles B. Carrington, M.D.

ABSTRACT **Clinical, physiological, roentgenographic, and histological data concerning 502 patients who had open biopsy for chronic "interstitial" lung disease were reviewed. Mortality was 0.3%, the rate of complications was 2.5%, and the diagnostic yield was 92.2%. A modified Chamberlain approach in the second interspace is preferred for easy access to all lobes and mediastinum. Brief tube drainage is mandatory. Atelectasis and hemorrhage in the specimen are prevented by avoiding palpation and clamps, by delineating the wedge during full inflation, and by instant fixation. Customary biopsies of the tip of the lingula or middle lobe are avoided because these are common sites of inflammation, scarring, and passive congestion. Often, the most abnormal regions are biopsied apparently to aid the pathologist. Such selection has been the most important cause of meaningless histological findings and poor pathological, physiological, and roentgenographic correlations because these regions usually show end-stage disease of unrecognizable origin. Average lung is more likely to show an active and recognizable process.**

The pulmonary disorders referred to as diffuse, miliary, infiltrative, or interstitial have a number of features in common. The presenting symptom usually is dyspnea. Examination may reveal only dry crackles. The roentgenogram usually shows diffusely dispersed rounded, linear, or ground-glass opacities. Physiologically there is impaired oxygen exchange initially with well-maintained mechanics of breathing. These findings are not specific and, therefore, the diagnosis must be based on other aspects of the examination. Careful history taking is rewarding in about one-third of the patients [5, 13]. Occasionally, physical or laboratory examination may provide a lead. In approximately a third of the patients, however, lung biopsy becomes necessary because among the 200 more or less distinct infiltrative disorders, many are unrelated to environmental insults, have no extrapulmonary manifestations, and are not associated with specific secretions [5].

Our interest in diffuse infiltrative disease began 30 years ago when we organized a prospective study of clinical, physiological, and roentgenographic features, and our pathological material has undergone constant review. During recent years this group of disorders has received increasing attention, perhaps because of clarification of certain etiologies and refinement in the description of histological patterns. Also, a growing concern in environmental disease and immunological disorders has focused attention on interstitial diseases. Additionally, improved therapy, including effective antibiotics, antiinflammatory agents, immunosuppressive drugs, and pulmonary lavage, has justified the search for more precise diagnosis. Finally, the emergence of transbronchial biopsy has stimulated discussion concerning the unsolved questions of indications, specificity or diagnosis, and cost/benefit ratios. As a result, we now have 1,612 such cases on file, which represent 22.1% of all pulmonary patients seen in consultation since 1950.

This study was undertaken (1) to describe our technique of lung biopsy as it evolved over the

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From the Department of Surgery, Boston University School of Medicine, Boston, MA, and the Department of Pathology, Stanford University School of Medicine, Palo Alto, CA.

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years, (2) to determine mortality and morbidity, (3) to ascertain diagnostic yield, and (4) to review diagnostic failures in the light of discrepancies with clinical, physiological, or roentgenographic data. We also compare the results reported here with those of alternative approaches to lung biopsy, especially the transbronchial route.

Material and Methods

Between July, 1950, and January, 1980, 502 patients were referred to us, and 508 open lung biopsies were performed for diagnosis of chronic diffuse infiltrative lung disease. We included in this study all patients who had a thoracotomy primarily for diagnosis of chronic diffuse infiltrative lung disease. Excluded were patients having biopsy for solitary or isolated lesions, those with biopsy performed incidentally to other pulmonary or cardiac operation, those having lung biopsy during thoracotomy primarily for pleural or pericardial lesions, and patients having biopsy for *acute* diffuse pulmonary infiltrates defined as lesions present for less than a month.

The entire group served for review of diagnostic results and for correlation with clinical, roentgenographic, and physiological data. For analysis of mortality and morbidity we selected a subgroup of patients who were seen in consultation *before* operation. Those seen first *after* biopsy elsewhere, of course, had to be excluded from mortality studies.

Clinical Data

A conventional history was supplemented by a respiratory questionnaire based on that of the Medical Research Council [11, 14]. Added notations concerned environmental exposure, results of physical examination, selected laboratory investigations, and diagnoses.

Physiological Studies

The forced vital capacity (FVC), forced expired volume in one second (FEV_1), ratio of FEV_1 to FVC, and maximal voluntary ventilation were measured with a Stead-Wells spirometer. The single breath-diffusing capacity (Dsb) has been measured since 1954 according to the method of Ogilvie and co-workers [34], and more recently with an automated system [19]. Normal values for the spirometric data were those of Kory and associates [29], and for Dsb we used our regression equations [19]. The functional residual capacity (FRC) was measured by 7-minute helium rebreathing, and residual volume and total lung capacity (TLC) were calculated. An abbreviation terminated by a percent sign will indicate the percent of predicted values, for example FVC%. The technical details, methods of analyses, precautions, and calibration for all of these procedures were those recently adopted by the Epidemiology Standardization Project [11]. Blood gases, alveolar-arterial oxygen pressure difference ($P[A\text{-}a]O_2$), the ventilation equivalent for oxygen, and diffusing capacity (Dss), were measured during steady state at rest and, whenever possible, during steady state treadmill exercise by methods previously described [8, 12, 42].

Roentgenographic Observations

The appearance of preoperative chest roentgenograms was coded retrospectively, without knowledge of clinical information. We used the International Classification of Radiographs of the Pneumoconioses [26], which provides for description of the size of rounded (p, q, r) and linear-irregular (s, t, u) opacities, their location in 6 zones and their severity (profusion) in 11 steps from normal (0/0) to most severe (3/4). To adapt this scheme for description of all types of diffuse infiltrative diseases, we have added notations for reticulonodular patterns [6] and for ground-glass shadowing (alveolar pattern) [17, 18].

Pathological Observations

All sections were reviewed by one of us (C. B. C.), again without knowledge of clinical data. The technical quality of the sections was described as satisfactory, some problems, or unsatisfactory. Morphological changes were graded for each of several components of exudation, scarring, foreign material, and others. Final entries included a principal diagnosis and sometimes alternate diagnoses, prediction of prognosis, anticipated response to therapy, and, relevant to this study, an estimate of functional impairment based on judgment of the overall severity of the anatomical lesion [5, 6]. The confidence with which the principal diagnosis was made was graded on a scale of 1 ("classic lesion") to 5 ("no features favoring one diagnosis over others in the differential").

Lung Biopsy

A "formal" posterolateral thoracotomy was used initially and occasionally until 1963 [16]. Beginning in 1952, a small thoracotomy proposed by Klassen and associates [28] became an alternative. Since 1965 we have used an anterior approach similar to the mediastinotomy suggested by Chamberlain and McNeill [7, 33] but with the following differences: the incision is intercostal, thus precluding the need for resection of cartilage; it is slightly more lateral, obviating ligation of the internal mammary artery; and the pleura is always opened.

Under general endotracheal anesthesia, with the patient supine, a transverse incision 4 to 7 cm long is made over the second anterior interspace beginning medially about 2 cm from the sternal border. The pleura is opened laterally, the internal mammary artery is identified, and the incision is carried medially to that point. An infant-sized Tuffier or Finochietto retractor is placed between the second and third ribs and gently spread in stages. For cosmetic reasons or when the disease apparently is confined to the lower lung regions, an incision can be made in the submammary fold. Breast tissue is elevated and the incision is made in the fourth interspace more laterally. This scar is invisible even with a two-piece bathing suit.

The lung is allowed to collapse, and the easily exposed portions—the anterior segment of the upper lobe and the middle lobe and, with gentle retraction, the superior segment of the lower lobe and apex of the upper lobe as well as the anterior mediastinum—are inspected and gently palpated. More and less severely diseased lung regions are identified, and an *average* region is selected for biopsy. Most often this is the inferior margin of the anterior segment. When in doubt, less rather than more diseased lung is selected or two biopsies are obtained. So-called noncrushing clamps are never used on the lung. Rather, two stay sutures are placed at the margins of the selected triangle, which measures about 4 × 3 cm. The lung is inflated until it fills the thoracic cavity and patches of atelectasis have disappeared. Two narrow Carmalt or other curved clamps are applied, and, very quickly, two-thirds of the inflated specimen is excised and, within a second, placed in 10% buffered formalin for light microscopy. The remaining tissue is then removed for other studies to be described.

The lung beneath one clamp is closed with a horizontal continuous overlapping mattress suture (cobbler's stitch) of 3-0 chromic gut. The clamp is removed, and the wound is oversewn with an interlocking suture. The tissue beneath the second clamp is treated similarly. The wound is checked for air tightness under warm saline solution with positive airway pressure that causes complete inflation. Enlarged hilar, paratracheal, or other nodes or abnormal pleura and pericardium may be biopsied. Anesthesia is discontinued at this time. Invariably, a small 16F to 20F catheter is placed in the lateral margin of the wound and connected to underwater-seal drainage. The lung is fully inflated, and the wound is closed in layers. Low-flow oxygen is given for a few hours to hypoxemic patients and those with pulmonary hypertension. Most customary postoperative measures, including intermittent positive-pressure breathing, frequent blood counts, intravenous administration of fluids, and "prophylactic" antibiotics are avoided. Emphasis is on bronchial toilet, encouraging cough and early mobilization [20]. A chest roentgenogram with the patient in the upright position is made the following morning. With full lung expansion, the tube is removed and ambulation is encouraged. Return home or to the medical service usually is possible three to four days after operation.

Processing of Tissue

After overnight fixation, the tissue stored in formalin is cut into two or three pieces with large presenting surfaces and then is embedded. Routinely, sections are stained with hematoxylin and eosin, Verhoeff's elastic tissue stain, periodic acid–Schiff reaction, and one of the ferrocyanide reactions for iron. Additionally, the sections are always examined under

Table 1. Type of Incision, Mortality, and Complications in 360 Patients Having Open Lung Biopsies[a]

Mortality and Complications	Small Anterior (N = 300)	Standard Posterolateral (N = 60)
Deaths within 30 days (0.3%)	1	0
Major complications (2.5%)		
Localized empyema	1	0
Intercostal neuralgia	0	1
Respiratory insufficiency[b]	2	2
Myocardial ischemia[c]	1	0
Pulmonary edema[c]	1	0
Lung hernia requiring revision[d]	1	0
Minor complications (2.5%)		
Minor wound infection[d]	1	1
Transient pneumonitis	2	0
Late pleural effusion	2	0
Subcutaneous sinus, 10 days[d]	2	0
Muscle adhesions requiring revision	1	0

[a] The 360 of 502 patients who were seen before lung biopsy.
[b] All 4 patients had complicating severe emphysema.
[c] Patient also had mitral stenosis.
[d] All these patients were on high-dose corticosteroids before and after operation.

high-intensity polarized light. Special stains for various organisms and histochemical studies are obtained when indicated. The remaining third of the wedge is divided into at least three portions in the operating room. Invariably, one fragment is ground under sterile conditions and submitted for aerobic and anaerobic culture for bacteria, fungi, and mycobacteria. A second portion is submerged in glutaraldehyde and cut into 1 mm^3 cubes for electron microscopy. And the last portion is plunged into a vial containing Tissue-Tek O.C.T. compound, frozen in a mixture of dry ice and isopenthane, and stored at −60°C for possible immunofluorescent studies.

Results

Clinical data and pathological material were available for all 502 patients. Chest roentgenograms were reviewed for all but 18 patients whose roentgenograms had been sent elsewhere. All patients had physiological evaluation at some time but studies shortly before biopsy that were meaningful for correlation were available for only 358 patients.

Among the 502 patients, 360 were seen by us before operation; this was the subgroup used for mortality and morbidity studies. Most of them were operated on at our hospitals by one of us (E.A.G.) or a colleague. A few, subsequent to evaluation, elected to undergo operation elsewhere.

Operative mortality and complications in the 360 patients seen before operation are described in Table 1. All patients until 1952, and a few subsequently—a total of 60 (16.7%)—had a standard posterolateral thoracotomy. Small anterior approaches were used in all others. There was 1 death (0.3%) within thirty days. It occurred in 1957 in a severely ill, 60-year-old man who proved to have bronchiolar alveolar cell carcinoma and multiple pulmonary emboli. There were 9 major complications (2.5%) but only 3 had any important consequences. In 1 patient, an intercostal neuralgia developed after a standard thoracotomy. There was 1 localized empyema requiring secondary drainage, and in 1 patient, a poor muscle closure resulted in a subcutaneous hernia of a lung bulla requiring repair some weeks later. All 4 patients who required temporary assisted ventilation had complicating severe emphysema. Among the 9 minor complications (2.5%) there were 4 wound infections or briefly draining sinuses. All of the latter patients had received high doses of corticosteroids before and after operation (see Table 1).

Functional alteration as the result of operation could be evaluated when preoperative studies were performed within a few weeks before operation and postoperative studies 2 to 3 months after operation to assure full recovery, when there was no treatment during this interval, and when the disease was entirely stable. We found 39 patients who corresponded to all of these criteria. Most of them had pneumoconioses, untreated chronic interstitial pneumonia, stable sarcoidosis, or hilar nodes only (29). Their mean FVC% was 74.6 ± 18.7 before operation and 73.4 ± 17.7 six weeks to 3 months after operation, for a mean loss of 1.3%. And these values for Dsb% were 59.4 ± 26.7 before and 59.0 ± 24.3 after operation, for a mean loss of 0.4%. These changes were not significant by t test ($p > 0.05$).

Roentgenographically visible residuals of operation were coded as "biopsy changes" from roentgenograms obtained 3 months later. Usually they consisted of minimal blunting of the costophrenic angle, slight elevation of the hemidiaphragm, a unilateral basal ground-glass appearance, or new small localized densities. One or more such residuals were recorded in 12% of roentgenograms after a modified Chamberlain-type incision in the second interspace. They were seen more often, in 65%, after a low or submammary incision in the fourth or fifth interspace. Some of the most severe changes were seen on roentgenograms of patients who had biopsy elsewhere with an automatic stapling device.

Diagnostic Results

The diagnostic groups, together with some of the major disorders, are arranged in Table 2 according to a classification we have used recently [5]. Three major categories—sarcoidosis, the pneumoconioses, and the interstitial pneumonias—accounted for more than one-half (53.2%) of all cases, which is according to the experience of others. The relative frequency of some other disorders differed from that reported in recent series [1, 3, 30, 35, 38]. There were fewer infections because we excluded

Table 2. Major Diagnostic Groups among 502 Patients Having Open Biopsy

Group	No. of Patients[a]
Infections	16 (3.2)
Miliary tuberculosis	5
Fungal	7
Other	4
"Allergic"	34 (6.8)
Chronic eosinophilic pneumonia	17
Allergic alveolitis	9
Unclassified and other	8
Granulomatous	83 (16.5)
Sarcoidosis	63
Wegener's and lymphomatoid	6
Other	14
Pneumoconioses	74 (14.7)
Asbestosis	31
Silicosis and coal workers	18
Berylliosis	16
Other	9
Interstitial pneumonia	130 (25.9)
Usual interstitial pneumonia	64
Desquamative interstitial pneumonia	50
Acute interstitial pneumonia	8
Other	8
Malignant	26 (5.2)
Lymphoma	4
Bronchiolar alveolar carcinoma	7
Diffuse carcinomatosis	12
Other	3
Unusual	43 (8.6)
Eosinophilic granuloma	17
Pulmonary alveolar proteinosis	11
Miscellaneous	15
Cardiac	6 (1.2)
Pulmonary vascular	19 (3.8)
Bronchiolitis obliterans	11 (2.2)
Honeycombing	17 (3.4)
Nonspecific	28 (5.6)
Nonspecific fibrosis	14
Chronic bronchiolitis	9
Other nonspecific	5
Pleural disease only	11 (2.2)
Normal lung	4 (0.8)
Total	502

[a] Number in parentheses is percent of patients involved.

from this series biopsies performed for acute disease. Allergic alveolitis is uncommon in our area and, with improved history taking and serological studies, these reactions increasingly are recognized without biopsy. Bronchogenic and metastatic carcinoma have figured prominently in previous series. In this study we focused on biopsies for diffuse or interstitial disease, and therefore 47 biopsies for solitary or multiple nodular lesions were excluded. Sarcoidosis appeared more frequently because in recent years we have preferred the modified Chamberlain approach to mediastinoscopy.

The diagnostic yield should be the standard of comparison for different series and methods, but actually the yield is not easily defined. Lung biopsy should provide a diagnosis in those disorders whose current basis for definition is in anatomical terms. However, such a description rarely includes the causal agent [36]. Furthermore, the rate of "diagnostic" results depends on the rigor of the pathologist's diagnostic criteria [5], on case selection, and on correlation of biopsy findings with clinical, immunological, roentgenographic, and other data. We elected to consider only the diagnoses that were recorded by the pathologist without knowledge of clinical data. Therefore, in the results reported in Table 2, no distinction was made as to etiology when this was not apparent from microscopy. For example, allergic alveolitis is not further categorized and the interstitial pneumonias are not subdivided according to relationship to systemic disease.

With these limitations in mind, there were 28 patients with a nonspecific diagnosis and 4 that showed normal lung (see Table 2), for an obvious failure rate of 6.4%; and in 11, the disease proved to be largely of the pleura. Honeycombing, in 3.4% of patients, accurately reflects the appearance of the lung. However, it is a nonspecific diagnosis because it describes the end stage of a variety of disorders ranging from eosinophilic granuloma to interstitial pneumonia [2].

An additional consideration in the evaluation of diagnostic biopsies is the confidence with which the diagnosis was made. In this study, the "confidence" was rated on a scale of 1 to 5, with 5 indicating that the histological appearance did not favor one diagnosis over others in the differential or that the appearance did not match that of any previously described entity. Among the 443 diagnoses that were graded, there were 7 with a grade of 5. In these instances, biopsy was not diagnostic and was helpful only in a negative sense in that it may have ruled out certain other diagnoses that were under consideration. The best estimate of diagnostic yield in this series was 92.2%.

Technical quality of the biopsy specimen was graded as "satisfactory" in most instances, but in 59 instances (11.8%) there were problems that distracted from the histological examination.

- Operative Problems
  - Size
    - Too small
    - Subpleural only
  - Selection
    - Nonrepresentative nodule
    - Worst disease (incompatible with life)
    - Worst disease (nonspecific honeycombing)
    - Atypical: tip of lingula or middle lobe
    - Lesions missed (rare)
  - Handling
    - Crushed and/or operative hemorrhage
- Postoperative Problems
  - Specimen collapsed, atelectatic
  - Section too thick or torn
  - Specimen cut in small pieces
  - Poor stain or important stains missing

Most often problems arose because the biopsy was too small. Also, a specimen containing only subpleural tissue was difficult to evaluate especially if there was pleuritis. Another criticism referred to site selection. Sometimes this was evident to the pathologist when the specimen consisted of nothing but fibrous tissue or extreme honeycombing; then, if the biopsy had been representative, the condition would not have been compatible with life. More often, a nonrepresentative sample was detected during subsequent comparison of "pathological severity" with clinical, physiological, and roentgenographic data.

Proper handling of the specimen during and immediately after biopsy is discussed in the section on "methods." Disregard of these precautions not uncommonly resulted in operative hemorrhage or a specimen crushed beyond repair, which hindered evaluation of fine detail. The importance of clamping the inflated lung and of immediate fixation is illustrated by Figure 1.

Correlation with Physiological Data

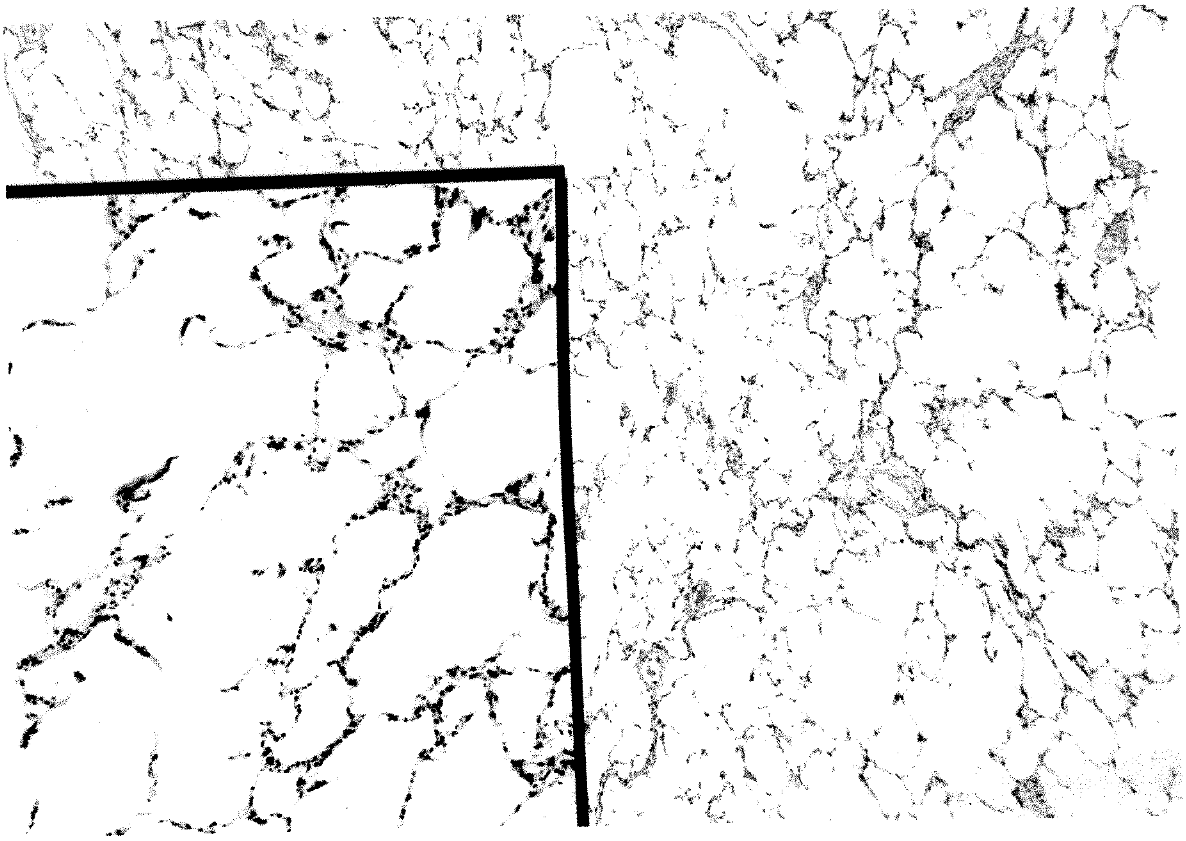
There were 358 of 502 patients who had studies of mechanics of breathing and Dsb within a few weeks before operation, and 156 of these—the less severely ill—also had steady state studies during treadmill exercise. The type and severity of impairment varied widely but, on average, corresponded closely to the findings originally ascribed to what used to be called the "alveolar capillary block" syndrome. The most meaningful studies with respect to restrictive disease and impaired gas exchange are displayed in Table 3. The mean FVC% was reduced to 70.3 but many patients with early disease had a normal FVC. And, contrary to most texts, the TLC% was normal more often than not (mean, 92.1 ± 26.5% of predicted). Reductions of Dsb and Dss during exercise often occurred early. These values averaged two-thirds of normal; and the fraction of carbon monoxide removed was reduced to one-half of normal. Most consistent was the increase of exercise P(A-a)O_2, with a mean of 41.3 mm Hg compared with a normal range of 5 to 15 mm Hg.

Correlations of these data with the estimates of functional impairment from histology (pathological severity) were imperfect, but all Spearman's rank correlations (r_s) were highly significant ($p < 0.001$). The highest r_s were found for Dsb% and for exercise P(A-a)O_2 (see Table 3). We displayed the relationship between pathological severity and P(A-a)O_2 and then reviewed histological material and clinical as well as physiological data pertaining to those few points that showed a discrepancy of more than 2 steps in pathological severity (Fig 2). Among the 6 patients with severely abnormal lungs and relatively low P(A-a)O_2, the discrepancy almost always was due to a sampling problem in that the surgeon had selected for biopsy the most severely diseased region of the lung. The opposite situation, an elevated P(A-a)O_2 with only slight histological changes was observed in 8 patients (see Fig 2). Some of these had primarily pleural disease and others had complicating emphysema.

There was no correlation between preoperative functional impairment and postoperative respiratory complications. Indeed, before operation 23 patients had an FVC% of less than 40, 52 patients had a Dsb% of less than 40, and 38 had a partial pressure of arterial oxygen of less than 40 mm Hg. None of these patients required assisted ventilation. There was, however, a relationship between the degree of complicating obstructive disease and postoperative respiratory decompensation: all 4 patients who required prolonged resuscitation (see Table 1) had a greatly reduced FVC/FEV_1 ratio, and 3 of the 4 had hypercapnia at rest.

Correlation with Roentgenographic Appearance

Our term *pathological severity* refers to an estimate of *functional* impairment, and this estimate was not designed to reflect the severity of roentgenographic changes. Indeed, there are many reasons why microscopic observation might not reflect the gross changes seen on the roentgenograms. However, in this study, biopsy was most often prompted by an abnormal chest roentgenogram. Therefore, a plot was prepared relating roentgenographic and pathological severity (Fig 3). Adequate roentgenograms obtained within a few weeks before biopsy were available for 354 patients. The overall severity of roentgenographic opacities correlated highly with pathological severity (r_s = 0.47, $p < 0.001$). However, a number of individual discrepancies were observed. In 11 patients, the pathological severity was graded 4 or 5 yet the roentgenograms were categorized as 1/2 or less. The reasons usually were obvious: for example, in 3 patients, the disease was localized with a relatively normal roentgenogram, and the biopsy was from the area of infiltration; in 3 others the severe microscopic abnormalities referred primarily to the vasculature or small airways, and these changes, of course, were not reflected by the roentgenogram; and in 2, the disease clearly had progressed during the interval between roentgenography and op-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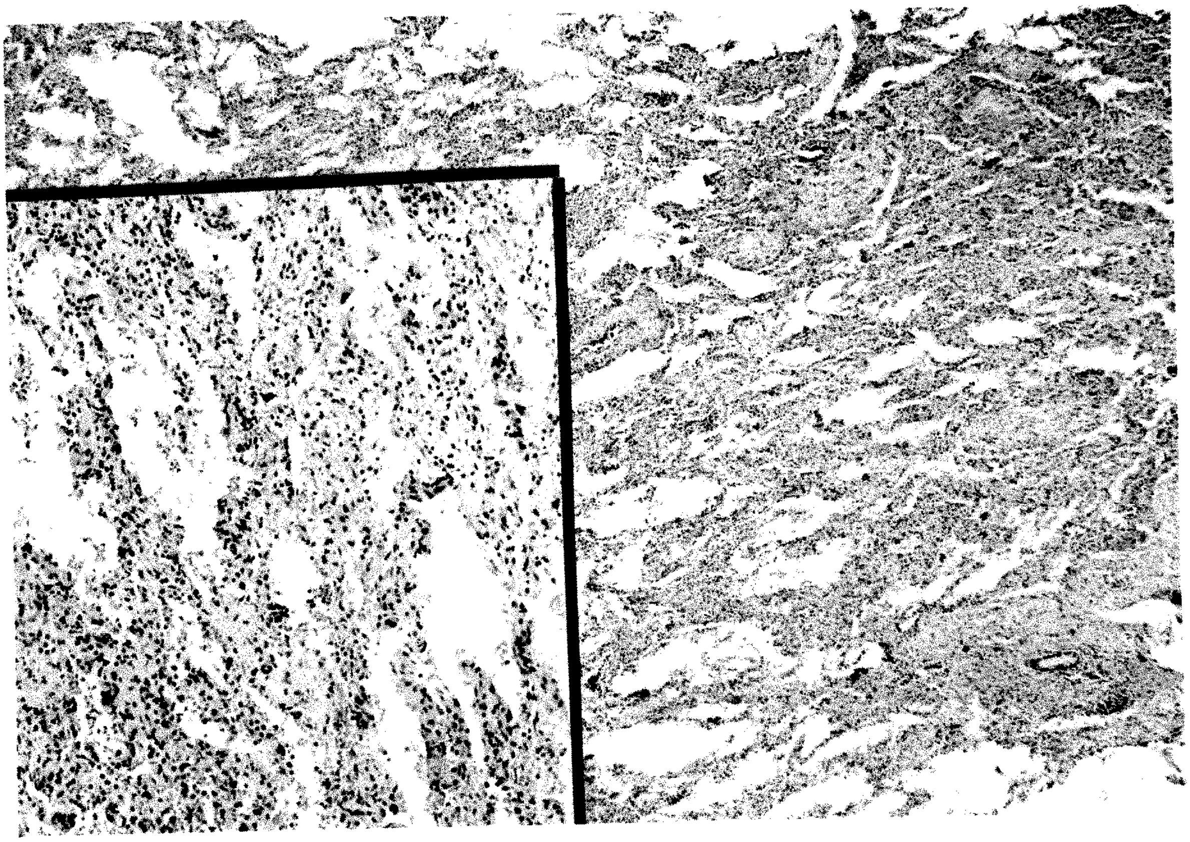
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Table 3. "Pathological Severity": Correlation with Physiological Data and Roentgenographic Severity

Determination	No. of Patients	Predicted Normal Range	Determination Mean ± SD	Determination Range	r_s with Pathological Severity	Significance of r_s (p)
FVC (% predicted)	358	100 ± 20	70.3 ± 21.0	21–130	−0.39	<0.001
TLC (% predicted)	345	100 ± 20	92.1 ± 26.5	25–213	−0.34	<0.001
Dsb (% predicted)	264	100 ± 20	61.5 ± 24.1	9–144	−0.52	<0.001
Dss (ml/min/mm Hg), exercise	155	25–35	17.6 ± 10.7	4–38	−0.32	<0.001
$P(A\text{-}a)O_2$ (mm Hg), exercise	156	5–15	41.3 ± 17.1	8–89	0.58	<0.001
Fraction CO removed, exercise (%)	155	>45	26.0 ± 10.0	9–62	−0.37	<0.001
ILO radiographic severity	354	0/0–0/1	2/1	0/0–3/4	0.47	<0.001

r_s = Spearman's rank correlation; FVC = forced vital capacity; TLC = total lung capacity; Dsb = single-breath diffusing capacity; Dss = diffusing capacity with steady-state exercise; $P(A\text{-}a)O_2$ = alveolar-arterial oxygen pressure difference; CO = carbon monoxide; ILO = International Labor Organization.

eration. Overreading of roentgenograms in view of the histological appearance was much more common (see Fig 3). Review suggested that in the majority of such instances, the disease was associated with small rounded or reticulonodular opacities, 13 patients with sarcoidosis, 2 with anthracosilicosis, and 1 each with eosinophilic granuloma and histoplasmosis. These rounded opacities caused striking roentgenographic shadows but histologically they were isolated lesions with much intact, intervening lung tissue; and physiological abnormalities were minimal. We have noted previously the roentgenographic and physiological discrepancies in such patients [6, 18]. In a few other patients, severely coded roentgenographic changes actually proved to be due to pleural changes, hence the discrepancy with lung histology.

A finding of normal roentgenograms in patients with substantial interstitial lung disease was the most striking discrepancy in this series [10]. Figure 3 shows that among 354 patients with classifiable pathological severity and adequate preoperative roentgenograms, the lung fields in 56 (15.8%) were classified as within normal limits (categories 0/0 and 0/1). The diagnoses and pathological severity are shown in Table 4. Sometimes the reason for the normal roentgenogram was apparent. In some patients with sarcoidosis and asbestosis, the lesions were so slight, so few, or so small that that pathologist's estimate of functional loss was also graded 0. Other patients had primarily pulmonary vascular or small airway diseases, which would not be apparent roentgenographically. The most striking roentgenographic and pathological discrepancies were seen in desquamative interstitial pneumonia and allergic alveolitis. Possible explanations are indicated in Table 5.

Comment

Lung tissue may be required for diagnosis mainly in three situations: with solitary pulmonary lesions, in chronic interstitial lung disease, and with certain pulmonary infections especially in infants unable to produce sputum. Recently two indications have been added: for suspected unusual infections related to immunodeficiency and for detection of fibrosis in the acute respiratory distress syndromes. Clearly, indications, choice of procedure, and

Fig 1. Illustrations to emphasize the importance of proper fixation. A wedge of lung was clamped with the lung fully inflated in a patient who was to have a lobectomy for bronchiectasis. One-half of the specimen (A) was immediately immersed in formalin as described in the text. Individual alveoli and other details are easily distinguished and are normal. The other half (B) was wrapped in a sponge moistened with saline solution and stored in the refrigerator with other specimens for transfer to the pathology laboratory. Here, at the same magnification as (A), many alveoli are collapsed, and it is now difficult to determine whether or not the alveolar walls are normal. Insets show a portion of A and B at a higher magnification. (Both H&E.)

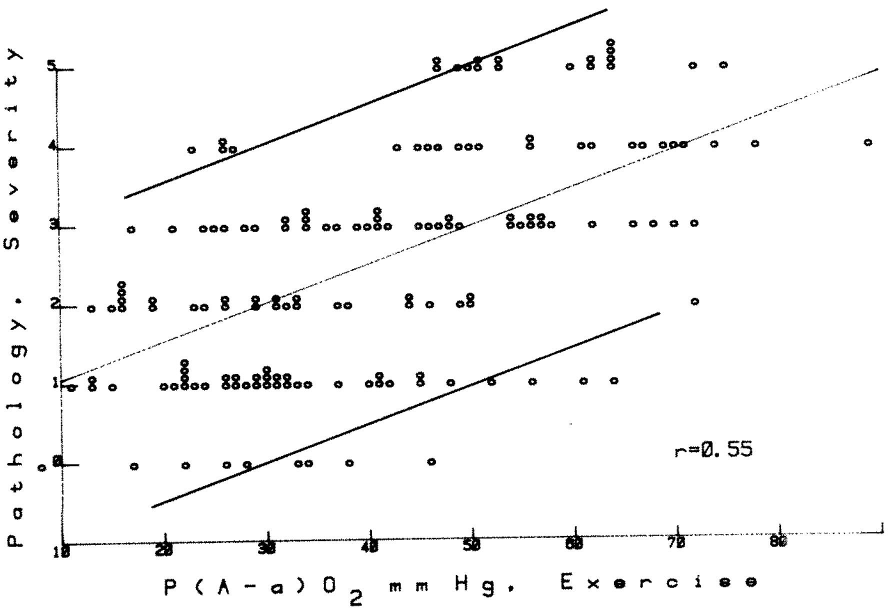

Fig 2. Computer-generated plot relating the pathologist's estimate of functional impairment (Pathology Severity) *on a scale of normal (0) to severe (5) to the alveolar–arterial oxygen pressure difference* (P[A-a]O_2) *during exercise. When the points fell outside the two extreme lines, the data were reviewed. Reasons for these discrepancies are discussed in the text.*

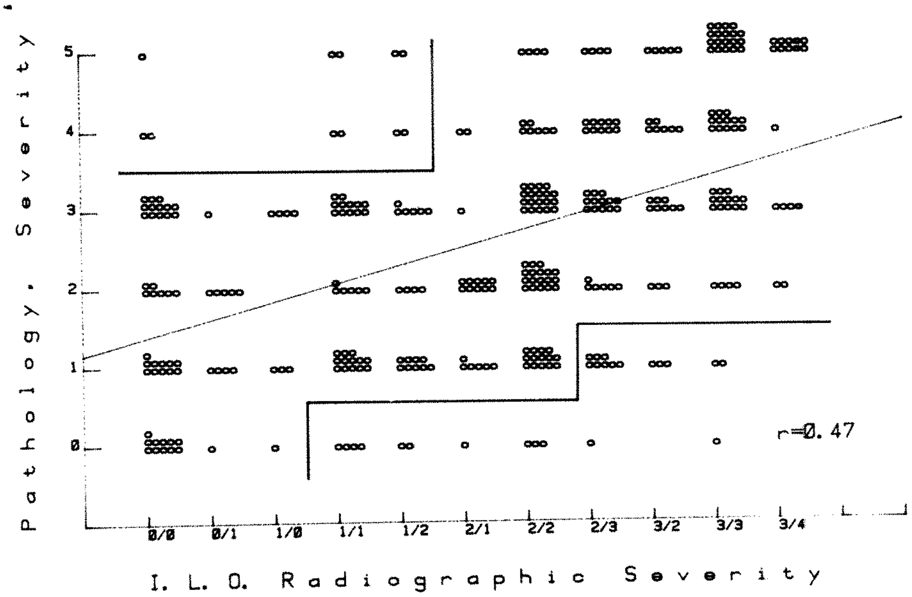

Fig 3. The pathologist's graded estimate of functional impairment, as in Figure 2, is compared with the severity of roentgenographic shadowing. The overall profusion of rounded, irregular, or ground-glass opacities was graded from normal (0/0) to most severe (3/4) on an 11-point scale. Cases with marked discrepancies outside the two extreme lines were reviewed.

Table 4. Diagnosis and "Pathological Severity" in Patients with Normal Roentgenograms[a]

No. of Patients	Diagnosis	"Pathological Severity" 0	1	2	3	4	5	Probable Reason for Normal Chest Roentgenogram
7	Sarcoidosis	6		1				1. Discrete parenchymal lesions too small and too few to be visualized
2	Miliary tuberculosis		1	1				2. Discrete lesions too small to be discerned individually, unappreciated diffusely increased density
8	Asbestosis	5	3					3. Interstitial reaction too slight to be appreciated, or obscured by pleural reaction
								4. Diffuse interstitial lesion leading to uniform reduction in alveolar volume; relative airlessness not appreciated
2	Patchy fibrosis		2					Explanations 3 and 4
4	Usual interstitial pneumonia		1	1	2			Explanations 3 and 4
1	Drug reaction			1				Explanations 3 and 4
5	Allergic alveolitis		1		3		1	5. Explanations 2 and 4
12	Desquam. interstitial pneumonia	1	3	2	6			6. Uniform loss of alveolar volume not appreciated
1	Lymphoma			1				Explanation 6
1	Eosinophilic pneumonia				1			Explanation 6
2	Bronchiolitis obliterans			1		1		7. Primarily airways disease
2	Chronic bronchiolitis		2					Explanation 7
2	Multiple pulm. emboli				1	1		8. Primarily vascular disease
2	Idiopath. hypertension		2					Explanation 8
2	Venoocclusive disease			2				Explanation 8
1	Talc emboli				1			Explanation 8
2	Lymphangioleiomyomatosis			1	1			9. Explanations 1, 7, and 8

[a] "Pathological severity," graded from 0 to 5, refers to pathologist's estimate of functional impairment; normal chest roentgenogram refers to immediate preoperative films read as 0/0 or 0/1.

evaluation of mortality and complications differ greatly in these five situations. This review deals only with biopsy for chronic diffuse or interstitial lung disease. Procedures performed for acute illness that had lasted less than a month were excluded. We did this because for patients in acute respiratory distress, indications for lung biopsy are controversial and because our principal aims could not have been achieved. We disagree with others who believe that mortality and morbidity associated with biopsy can be measured in a group of patients the majority of whom die within a few days [24]. Furthermore, diagnostic yield is difficult to evaluate because of the monotonous similarity of the diffuse alveolar injury and early fibrosis.

Lung biopsy by "formal" posterolateral thoracotomy has been performed sporadically for many years, and our first 60 patients were done in this way (see Table 1). However, this incision limits operation to good-risk patients, and entails much more time, blood loss, hospitalization, and morbidity, and, we think, it is now inappropriate for lung biopsy though it is still advocated by some [1]. Klassen and co-workers [28] in 1949 proposed a small anterior thoracotomy without intubation that actually was largely an extrathoracic procedure. Lung was herniated through the incision by positive pressure, grasped with a Duval clamp, and excised without allowing the lung to collapse. In our hands, this method entailed several difficulties including problems with anesthesia, inability to explore, which resulted in sampling problems, and often small, mangled specimens.

Table 5. Results of Lung Biopsy Procedures[a]

Type of Biopsy	No. of Series	No. of Patients[b]	Percent Mortality	Percent Complications	Percent "Diagnostic"
Needle core	9 (1964–74)	789	1.1	42.0	63
Drill	10 (1969–76)	551	0.5	44.0	72
Transbronchial	8 (1974–78)	1,289	0.2	12.8	72
Open	15 (1949–78)	2,290	1.8	7.0	94

[a] Abstracted from the review by Gaensler [15].
[b] Only patients with diffuse or interstitial disease.

The method described here evolved as the result of these experiences and because of occasional problems with low incisions now advocated by most surgeons. Incisions in the fourth or fifth interspace should be avoided in general, even when the roentgenogram shows most disease at the bases. At operation the lungs are small because they are at FRC and also because the patient is supine. Therefore, when there is marked restriction, a low incision exposes the diaphragm, the base of the lung cannot be well visualized, selection of lung tissue is impossible, and the mediastinum cannot be explored. Furthermore, as we have shown, low incisions much more frequently result in roentgenographic residuals. Finally, because of the usual predominance of interstitial pneumonias at the lung bases, low incisions tend to favor biopsy of the most diseased lung regions that often show nothing but honeycombing.

Most surgeons suggest incision over the roentgenographically determined site of greatest involvement "so as to anticipate the best yield"; and they select for biopsy the most abnormal lung regions apparently to help the pathologist or to avoid obtaining normal lung [9, 22, 33, 35, 37]. Our experiences detailed here suggest that such selection is the single most important cause of meaningless histological findings and of lack of pathological, physiological, and roentgenographic correlations. All too often, such regions of "greatest involvement" show nothing but end-stage disease of unrecognizable origin (see list, p 416). Average lung or, in patients with advanced disease, the least involved areas usually show the pathological process at an active and recognizable stage [27, 36].

The tips of the lingular segment or middle lobe have been favored sites for biopsy, apparently because this tissue is easily delivered into the wound and only a single clamp is required to delineate the specimen [3, 9, 40, 43]. This is unfortunate because these most dependent portions of the lung are common sites of inflammatory changes and scarring unrelated to the diffuse disease [35], and also they are excessively affected by passive congestion [31, 41].

Hemorrhage and atelectasis increase the difficulties of histological observations. Therefore, the lung tissue to be resected must be treated with utmost care. Palpation must be gentle, and application of "noncrushing" clamps such as a sponge-holding forceps, Duval lung clamps or Allis forceps, advocated and illustrated by many surgeons [3, 9, 21, 27, 28, 35, 37, 43], should never be used.

Several procedures have been proposed for prevention of atelectasis. Storage of the specimen in gaseous carbon dioxide in our experience has caused irregular and unreliable expansion. Cannulation of bronchioles under the dissection microscope with glutaraldehyde perfusion [4] is too difficult and time-consuming for routine use. Stockinger and Höfler [39] reviewed methods for maintaining inflation and suggested tissue entrapment by a double circular clamp. We have obtained the best results by single clamping and instant fixation (see Fig 1).

Lung closure with an automatic stapling device has been advocated [24, 25], and an increasing percentage of patients referred to us after operation elsewhere exhibit the indelible marks of such machines. The misadventures following a number of these operations have suggested that stapling in the present context is ill-advised. The two or three minutes saved are negated by the required larger incision. Also, selection of tissue for biopsy, sometimes at considerable distance from the incision, is more difficult. Stapling is more expensive, and it increases the chance of prolonged air leaks and hemorrhage. Finally, it is more wasteful of tissue. With the method described here there have been few complications and never a pneumothorax or hemothorax (see Table 1).

Tube drainage for at least twenty-four hours is imperative. Completely airtight closure cannot be accomplished following pneumonotomy, and even a small pneumothorax may prove fatal in patients with severe restrictive disease and pulmonary hypertension. Those who have advocated closure without a tube have changed their minds [27, 28] or subsequently have reported high mortality and morbidity related to pneumothorax, hydrothorax, and subcutaneous emphysema [27, 30, 40]. In five series in which no tube was used, the operative mortality among 891 patients was 3.5% and the rate of complications was 9.1% [1, 27, 35, 36, 40] while in seven series with drainage, reported during the same period, the operative mortality among 1,021 patients was only 0.9% and the rate of complications was only 4.1% [3, 9, 22, 23, 37, 38].

The combined thirty-day mortality of fifteen large series, which included 2,290 patients who underwent open biopsy for interstitial lung disease and which were reported during the last 30 years, was 1.8% (Table 5). However, almost one-half of all deaths were associated with terminal carcinomatosis. Exclusion of these patients reduced mortality to 1.0%. The combined complication rate of 7.0% was lower than for any of the closed biopsy procedures (see Table 5). The overall rate of diagnostic results for the fifteen series that we reviewed was 94% [15], which, predictably, was much better than for the closed biopsy methods (see Table 5).

The indications for lung biopsy have not changed: biopsy remains indicated when the lung disease is undiagnosed after a suitable workup. However, the interpretation of "suitable workup" has changed. Originally, it was held that open biopsy should not be resorted to until all other diagnostic procedures had been exhausted, presumably on the assumption that all other tests added together are less dangerous, less painful, and less costly than lung biopsy. Therefore, open biopsy was not advised until bronchoscopy and biopsy of lymph nodes (prescalene) and often of the liver, kidney, muscle, and sternal marrow had been performed and until roentgenographic procedures had encompassed at least laminagraphy, gastrointestinal series, barium enema, intravenous pyelography, and a skeletal series. Often many of these tests were repeated during several admissions. As a result, in our initial series an average 1.53 years elapsed between first notice of an abnormal chest roentgenogram and biopsy [16]. In retrospect, many patients could have been spared years of uncertainty, inactivity, large hospitalization costs, and many unpleasant procedures by earlier biopsy. Also, a number of the preliminary diagnostic tests are not without mortality and morbidity. Finally, in some instances, early positive diagnosis might have permitted treatment before the disease had reached an irreversible or fibrotic stage. We concluded that, in the absence of special leads, lung biopsy should be performed as soon as adequate history, clinical examination, skin tests, and thorough investigation of the sputum have failed to give a clue to diagnosis [16]. Since then, in our patients, the interval between discovery of the lesion and biopsy has been reduced to 2 to 3 months.

We have learned other lessons. For example, we no longer hesitate to perform biopsy if the chest roentgenogram is normal (see Table 4), and we now rely on pulmonary function studies, especially Dsb and $P(A\text{-}a)O_2$, to indicate the presence of interstitial disease. With increasing experience we have learned to recognize certain disorders without biopsy: chronic eosinophilic pneumonia is perhaps the best example [17]. Also, we no longer advise biopsy in elderly patients with extensive honeycombing on roentgenograms because in such patients, biopsy has made no contribution from either the diagnostic or the therapeutic standpoint.

Over the years, a number of "closed" procedures have been proposed for lung biopsy. A recent review [15] and our own experiences suggest that transthoracic needle core and drill biopsies entail all of the disadvantages of the closed procedures, that is, they yield a tiny, unselected specimen, yet the mortality and complication rate is greater than that of open biopsy (see Table 5). Indeed, certain disastrous complications including massive bleeding and air embolism are peculiar to these procedures. Therefore, they are no longer considered to be viable alternatives to the open procedure. Transbronchial biopsy, introduced by Anderson and co-workers [2], has gained enormous popularity with substitution of the fiberoptic for the rigid bronchoscope in 1974 [32]. It entails the lowest mortality of any lung biopsy procedure (see Table 5) and is less traumatic and certainly much less expensive. However, it has introduced new diagnostic problems for the pathologist because the specimen has all the features that open biopsy tries to avoid: it is unselected and exceedingly small, the lung tissue is crushed, and the specimen comes from regions immediately adjacent to bronchi. Histological changes variously termed fibrosis with or without inflammation, nonspecific reaction, or interstitial pneumonitis have emerged as the more frequent findings. Because of these unsolved problems, we conducted a prospective study comparing results of transbronchial biopsy with open biopsy [41a]. In 46 patients, transbronchial biopsy was diagnostic in 37% compared with 91% for the open procedure. Disorders with characteristic histology such as sarcoidosis or carcinomatosis were readily recognized by transbronchial biopsy in most instances. However, among specimens that by transbronchial biopsy showed nonspecific abnormalities, interstitial pneumonia, interstitial fibrosis, or normal lung, the actual diagnoses from open biopsies bore no relation to the diagnoses obtained by transbronchial biopsy. Clearly, it is a worthwhile preliminary to open biopsy in selected patients but impressions of interstitial pneumonia, nonspecific reaction, or fibrosis obtained by transbronchial biopsy are neither helpful nor reliable in establishing a morphological diagnosis in chronic infiltrative lung disease.

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Discussion

DR. GORDON F. MURRAY (Chapel Hill, NC): Diffuse lung disease is a common and perplexing problem, and diagnosis is greatly facilitated by obtaining pulmonary parenchyma for histological examination. Open lung biopsy is the standard for definitive diagnostic yield, and Dr. Gaensler in this extensive and beautifully detailed study has demonstrated that it can be done safely and accurately. Nevertheless, if similar results are attainable, a simpler technique—avoiding morbidity relating to general anesthesia and thoracotomy—is desirable.

Three years ago, I reported to the Society 40 consecutive patients who underwent flexible fiberoptic transbronchial lung biopsy to diagnose diffuse infiltrative lung disease. Specimens of lung parenchyma were obtained for histological study in every instance, and a pathological diagnosis was correctly established in 85% of patients.

All the procedures were performed using an Olympus fiberoptic bronchoscope, with the aid of biplane fluoroscopy and image intensification. In each case of suspected sarcoidosis or carcinoma, the diagnosis was confirmed. Importantly, no "opportunistic" infection was missed in immunologically compromised hosts. In only 2 patients were the ransbronchial biopsy results not accurate, and each of these patients subsequently was shown to have ymphoma.

The majority of our patients had pulmonary fibrosis. Although many surgeons are reluctant to accept a diagnosis of fibro-inflammatory disease established by transbronchial biopsy, undefined carcinoma or infection is uncommon. Utilizing open lung biopsy, unchanged or improved chest roentgenogram at 1 year, or both biopsy and roentgenogram as confirmatory diagnostic criteria, we have identified only 1 patient with unrecognized tuberculosis infection in the past 3 years.

The small transbronchial specimens are not adequate for histological classification of interstitial disease—as eloquently advocated by Dr. Gaensler and Dr. Carrington—particularly for a judgment of the prognosis and response to treatment. However, unless large amounts of tissue are needed for more sophisticated studies or to delineate the activity of the interstitial process, fiberoptic transbronchial lung biopsy is a safe and useful adjunct to the diagnosis of parenchymal lung disease. In any case, if the results of transbronchial biopsy do not support the clinical impression, an open lung biopsy must be performed.

DR. GAENSLER: I have no additional comments. Transbronchial biopsy is a safe and useful adjunct.

Notice from the American Board of Thoracic Surgery

The American Board of Thoracic Surgery will give a voluntary recertification examination in the fall of 1981. Diplomates interested in participating in this examination should maintain a documented list of their cardiothoracic operations performed two years prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings and other continuing medical education activities for the two years prior to application for recertification.

A recertification brochure has been prepared outlining the rules and requirements. It also contains information about applying for the voluntary recertification examination. The brochure has been mailed to all Diplomates except those certified in 1979 and 1980. If you have not received yours and wish a brochure, please write the American Board of Thoracic Surgery, 14640 E Seven Mile Road, Detroit, MI 48205.

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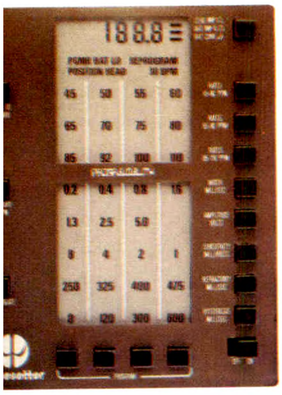

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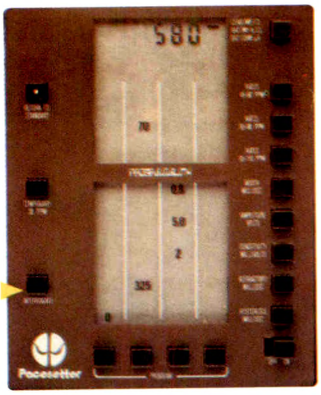

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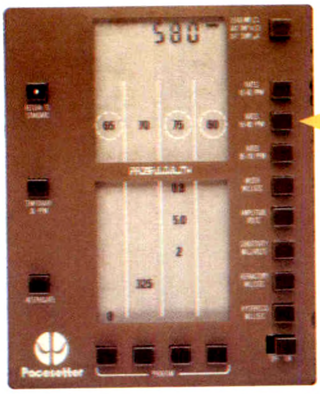

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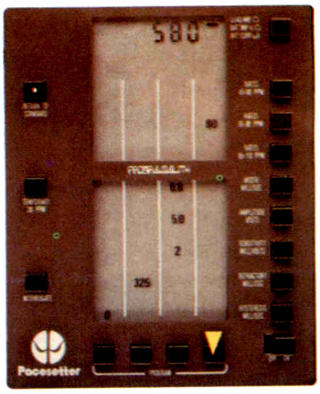

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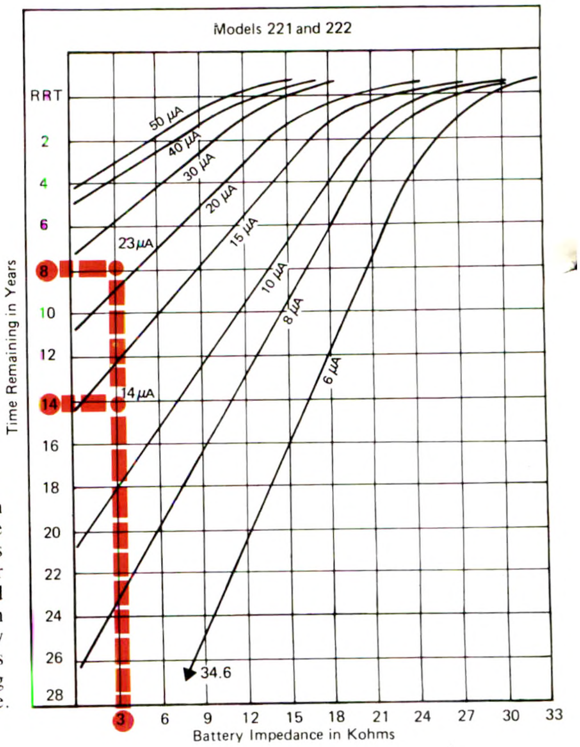

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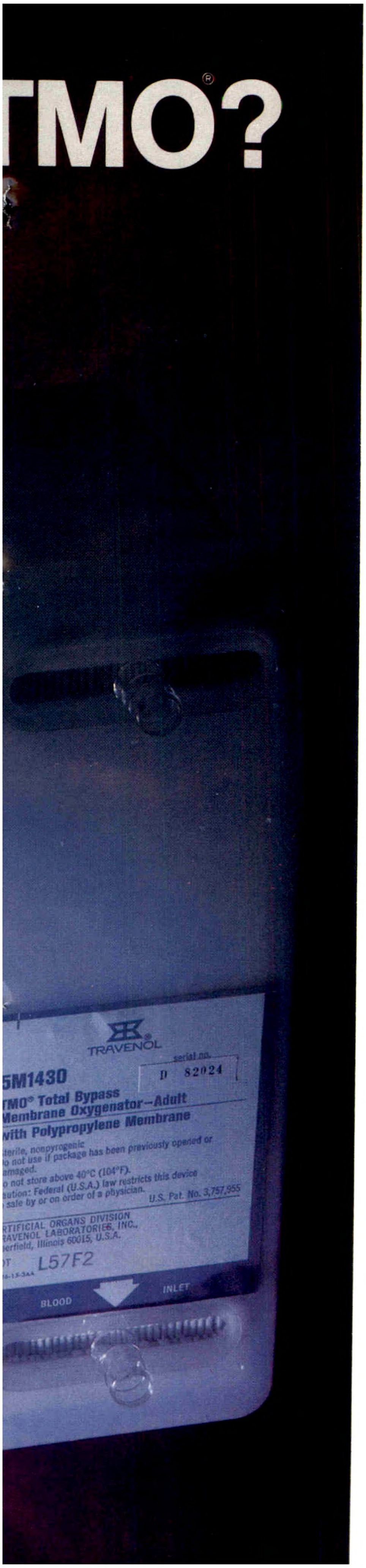
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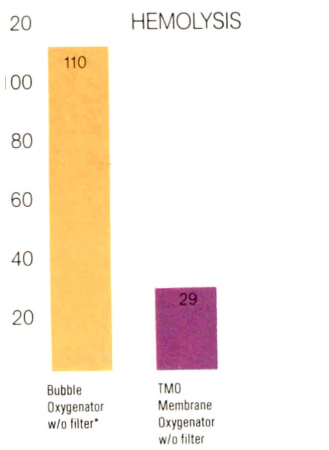
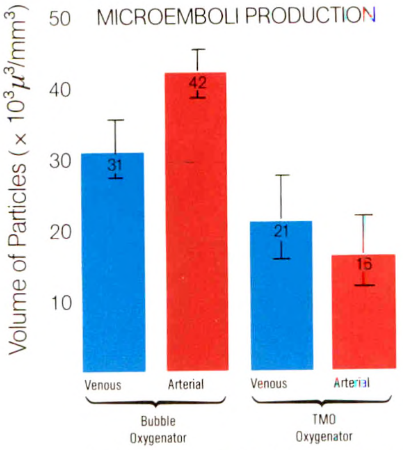


Source: Graph constructed from data presented in reference No. 1.
No. of cases - TMO Oxygenator 65
Bubble Oxygenator 70
*Bubble oxygenator w/filter - peak hemolysis 200 mg %



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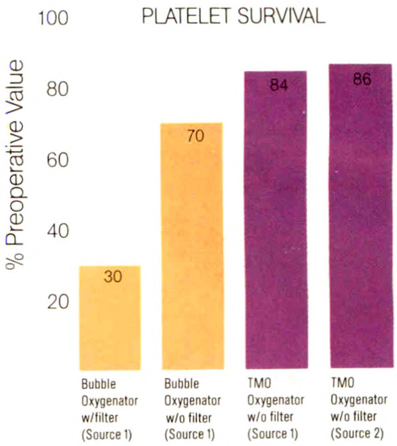

Source 1: Graph constructed from data presented in reference No. 1.
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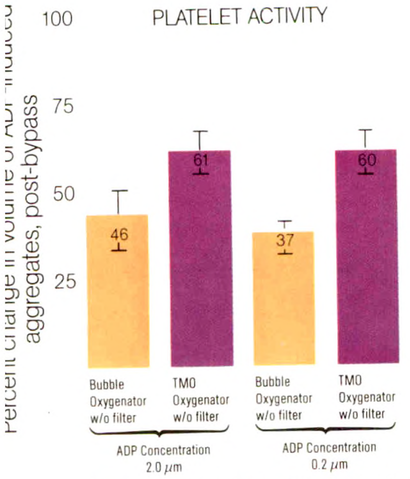

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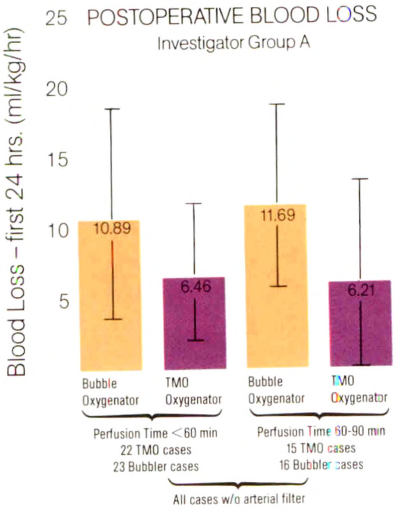

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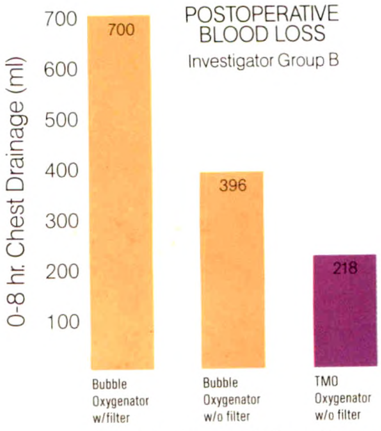

Source: Graph constructed from data presented in reference No. 1.

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NDICATIONS

The Travenol TMO Membrane Oxygenator is indicated for the oxygenation of blood and the removal of carbon dioxide from it in an extracorporeal circuit during total cardiopulmonary bypass at flow rates up to 6 liters/minute at altitudes not in excess of 5300 feet (1615 meters).

CONTRAINDICATIONS

Selection of patients as candidates for oxygenation is totally a medical responsibility and the outcome is dependent on many variables, including patient pathology and surgical and perfusion procedures.

In patients who are actively bleeding, medical judgment must be exercised in the use of the device. Benefits of oxygenation must be weighed against risks of total body heparinization. Oxygen requirements and transfer rates are influenced by many variables during perfusion.

WARNINGS

Evaluation of this oxygenator at elevated altitudes has shown inadequate outlet partial pressure for total bypass (apparently because of lower O partial pressure differences across the membrane). Until appropriate modifications are made, use of this device at altitudes above 5300 feet (1615 meters) is not recommended.

Use of blood suction devices must be limited where possible.

PRECAUTIONS

Adequate heparinization is essential. If the oxygenator is used in hyperbaric environments, both sides of the oxygenator must be referenced to the same pressure. The gas outlet port should remain open and free of any obstructions.

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Clinical Evaluation of Bronchopulmonary Lavage Using the Flexible Fiberoptic Bronchoscope

J. Garvey, M.D., J. Guarneri, Ph.D., F. Khan, M.D.,
and J. Goldstein, Ph.D.

ABSTRACT **Thirty-three patients had segmental and lobar bronchopulmonary lavage using three types of flexible fiberoptic bronchoscopes. A maximum volume of 300 ml of normal saline solution at room temperature was used. Lavage was effective for removing large numbers of alveolar macrophages (mean, 17 million) and proteinaceous material (mean, 0.18 mg per milliliter) that helped enhance the antibacterial properties of the macrophages. Transient shunting (mean fall in partial pressure of arterial oxygen, 65 mm Hg) and alveolar filling that reverted to normal in 3 hours were noted.**

The procedure averaged 45 minutes and was as simple as bronchoscopy. The larger the internal diameter of the bronchoscope (> 2.6 mm) the better suited it was for lavage. Sequential segmental lavage seems to offer the advantages of simplicity and technical ease over isolated lobar lavage with a balloon-tipped bronchoscope. It also has the advantage of simplicity over whole-lung lavage.

With the introduction of the flexible fiberoptic bronchoscope, safe and atraumatic access to the lower tracheobronchial tree has been possible [6]. The flexible bronchoscope has established itself as a major means of diagnosis and therapy in pulmonary diseases [16].

Minimal lavage of bronchi to obtain material for cytological and bacteriological examination is routine. Recent reports indicate the usefulness of more extensive lavage to obtain material for analyzing the protein components, lipid fraction, and cellular constituents of the lung and tracheobronchial tree [13, 15]. Therapeutic lavage also has been found useful in diseases such as pulmonary alveolar proteinosis, cystic fibrosis, and asthma [9, 10, 14].

It is likely that this new area of usefulness will become more important in the evaluation and therapy of many pulmonary conditions and in the investigation of the normal lung. For this reason, we undertook the following study to better define the technical requirements and safe clinical uses of effective bronchopulmonary lavage with the flexible fiberoptic bronchoscope.

Materials and Methods

The patient population consisted of three groups.

GROUP 1. Nineteen adult volunteers were evaluated by physical examination, chest roentgenogram, and complete pulmonary function tests. They were admitted to Queens Hospital Center, and bronchoscopy and bronchopulmonary lavage were performed by the transnasal technique. Bronchoscopy was done in the operating room the morning after admission. A chest roentgenogram was made in the recovery room, usually 1 hour after the procedure. Then, supplemental oxygen was given to each patient until he had recovered from the effects of the sedation and lavage. At this time, the volunteer was discharged from the hospital, between 2 and 4 PM in the afternoon.

GROUP 2. Eight patients were hospitalized and scheduled for bronchoscopy to evaluate nonpulmonary thoracic diseases such as carcinoma of the esophagus or mediastinal tumors. In these patients bronchoscopy was done through an endotracheal tube. Otherwise their evaluation was similar to that given the volunteers.

GROUP 3. Six patients were having diagnostic bronchoscopy for localized pulmonary dis-

From the Division of Cardio-thoracic Surgery, Long Island Jewish–Hillside Medical Center, New Hyde Park, and Queens Hospital Center Affiliation, Jamaica, and the State University of New York at Stony Brook, Stony Brook, NY.

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ease involvement, such as carcinoma of the lung. The area of lung lavaged was either not involved by the disease process or had minimal involvement, such as a Pancoast tumor or peripheral nodule. These patients had bronchoscopy through an endotracheal tube. Their treatment was similar to that of the other two groups.

All patients signed an informed consent as approved by the Human Subjects Review Committee of Long Island Jewish–Queens Hospital Center. Patients were premedicated with atropine (0.4 mg), diazepam (10 mg), and meperidine (50 mg) intramuscularly an hour prior to the procedure.

In the operating room, the electrocardiogram and blood pressure of each patient were monitored and an intraarterial line was inserted percutaneously into the radial artery. Blood gases were measured at several intervals with an oxygen mask* with a flow rate of 6 to 8 liters per minute: on room air; during bronchoscopy; during lavage; after bronchoscopy and lavage; in the recovery room; and subsequently on the ward with a 40% ventimask or room air. When the blood gases of the volunteers returned to normal, they were discharged. The patients stayed for treatment of the diseases.

Local anesthesia of the respiratory tract was obtained with 2% lidocaine spray in the nose and oropharynx and 4% lidocaine spray in the distal tracheobronchial tree. Bronchoscopy was performed with one of three bronchoscopes; the Olympus BF-B2, the Meditech FS/4.5/70 with SH-4F control handle, and the Machida FBS-6TL. The tip of the bronchoscope was positioned in either a segmental or lobar orifice, and sterile saline solution (0.9% sodium chloride) at room temperature was infused through the bronchoscope in 50 ml aliquots until a maximum of 300 ml was used. After each 50 ml infusion with a 50 ml syringe, the maximum amount of saline solution was aspirated through the syringe or through suction and collected in a trap.

The material recovered was centrifuged at 1,200 revolutions per minute for 10 minutes. The resultant supernatant fluid was separated from the cell pellet by decanting, thus dividing the aspirated material into an alveolar macrophage fraction and an acellular fluid fraction containing bronchopulmonary secretions. The acellular fraction was utilized directly or concentrated up to fifty times by positive-pressure ultrafiltration using a Diaflow UM-10 membrane. Bronchopulmonary lavage fluid was utilized immediately for phagocytosis studies [4] or stored in 1 ml aliquots at −70°C until used for biochemical and immunochemical analyses. The number of alveolar macrophages present in the cellular fraction was enumerated in a bright-line hemacytometer, and differential counts were made on Wright-stained smears. Macrophage viability was determined by their ability to exclude the dye eosin Y [5]. Last, total protein of bronchopulmonary lavage fluid (after removal of cellular fraction) was estimated by the Lowry method using human gamma globulin as the protein standard, and results were expressed as milligrams of protein per milliliter of fluid [2].

Results

The ages of the volunteers ranged from 18 to 50 years (mean, 30 years) (Table 1). Six did not smoke. The mean for the 13 smokers was 9.5 pack-years of smoking.

The Machida bronchoscope was utilized in 1 patient and the Meditech in the others. In 4 patients, a balloon attached to the sheath by the Meditech manufacturer was inflated and isolated lobar lavage was attempted. In the other patients, individual segments were lavaged. Mostly the right lower lobe was used. The maximum volume of saline solution used was 300 ml. The return averaged 50% for the group. There was no statistically significant difference between the returns for smokers or nonsmokers. Race, age, and sex did not appear to be significant.

The mean age for the group of patients without known lung disease was 50 years (Table 2). The mean return of lavage fluid was 34%. The Olympus bronchoscope was used in most of these patients, and lavage was segmental.

In the group of patients with carcinoma of the lung, the mean age was 60 years (see Table 2).

---

*Hospitek aerosol mask, manufactured by Hospitek, Farmingdale, NY.

Table 1. Data for Volunteers

Patient No.	Age (yr)	Vol. of Lavage Solution		Lavage Solution Recovered (%)	Roentgenographic Changes	Smoking History	Fall in PaO_2 (mm Hg)	Hours to Recovery of Prelavage PaO_2
		In	Out					
1	28	110	55	50	–	1 PPD	. . .	. . .
2	32	70	23	33	0	None	70	2
3	29	150	86	57	+	None	70	3
4	33	250	85	34	+++	1 PPD × 15	42	3
5	22	200	74	37	+	½ PPD × 5	28	4
6	33	250	93	37	++	1 PPD × 14	. . .	. . .
7	48	250	105	42	++	1 PPD × 5	77	2½
8	23	200	135	67	+	½ PPD × 4	108	4
9	18	250	136	54	+++	None	106	2
10	23	300	175	58	+++	1 PPD × 2	57	4
11	33	200	103	51	+	1 PPD × 17	33	1
12	20	250	131	52	++	None	140	1
13	28	300	175	58	+++	¼ PPD × 10	95	4
14	46	300	182	61	+++	1¼ PPD × 25	22	4
15	23	300	140	47	+++	None	32	4
16	27	150	47	31	0	½ PPD × 10	49	3
17	20	300	139	46	++	1½ PPD × 5	69	1½
18	30	300	145	48	+++	½ PPD × 10	. . .	. . .
19	50	300	117	39	++	None	21	1½

PaO_2 = partial pressure of arterial oxygen; ppd × X = packs per day × number of years.

All were smokers with an average of 30 pack-years. The left side was lavaged more frequently than the right, and the Machida bronchoscope was used in all but 1 patient. The mean lavage return was 37%.

In 13 of the 19 volunteers, chest roentgenograms made 1 hour after lavage showed alveolar filling. All 22 patients with lavage volumes greater than 200 ml showed changes on roentgenograms. The changes were graded from + to + + + depending on the degree of alveolar filling. Three patients given 200 ml also showed changes.

In the volunteer group, partial pressure of arterial oxygen (PaO_2) during lavage fell consistently, ranging from 21 to 140 mm Hg (mean, 65 mm Hg). Partial pressure of arterial carbon dioxide ($PaCO_2$) rose sporadically, and in half the patients fell or remained the same during lavage. Arterial blood gases on room air returned to normal within 1 to 4 hours (average, 3 hours).

In the patient groups, changes were present in 10 of the 14 on roentgenograms. Chest roentgenograms were made 24 hours after lavage in 5 patients, and all showed disappearance of the pulmonary infiltrate. The PaO_2 fell as much as 22 mm Hg (mean, 12 mm Hg). The $PaCO_2$ rose by a mean of 3 mm Hg.

Table 3 shows the percentage of macrophages and other cells in patients studied cytologically. Macrophage numbers ranged from 6.6 to 42.5 million (mean, 17 million). These macrophages were deemed viable by the dye-exclusion principle and had the morphological characteristics of alveolar macrophages described by others [18]. Acellular fluid fractions (bronchopulmonary lavage fluid) all contained levels of proteins detectable by the Lowry method of protein estimation. Protein content ranged from 0.10 to 0.35 mg per milliliter with a mean level of 18 mg per milliliter.

Comment

Ramirez and colleagues [12] introduced the technique of segmental irrigation for pulmo-

Table 2. Data for Patients with Carcinoma

Patient No.	Age (yr)	Vol. of Lavage Solution In	Vol. of Lavage Solution Out	Lavage Solution Recovered (%)	Roentgenographic Changes	Fall in PaO_2 (mm Hg)	Smoking History
PATIENTS WITHOUT LUNG DISEASE							
1	27	250	108	43	++	. . .	None
2	81	100	48	48	0	20	½ PPD × 50
3	72	150	52	34	0	7	1 PPD × 20
4	31	300	100	33	++	. . .	½ PPD × 10
5	56	300	148	49	++	. . .	2 PPD × 30
6	50	300	50	17	+	. . .	1 PPD × 25
7	33	250	92	35	++	16	None
8	48	300	70	23	+++	. . .	None
PATIENTS WITH CARCINOMA OF THE LUNG							
1	61	300	93	31	+	. . .	1½ PPD × 30
2	67	350	83	23	++	22	1 PPD × 25
3	65	150	50	33	0	. . .	1 PPD × 20
4	56	250	160	64	+	20	1½ PPD × 25
5	63	200	81	40	0	. . .	1 PPD × 30
6	50	300	125	42	+	10	1 PPD × 35

PaO_2 = partial pressure of arterial oxygen; PPD × X = packs per day × number of years.

Table 3. Protein and Cells Recovered from Bronchopulmonary Lavage

Patient No.	Percent Macrophages	Percent Lymphocytes	Percent Other Cells	Percent Bronchial Epithelial	Total Protein (mg/ml)	No. Macrophages Harvested ($\times 10^6$)	Macrophage Viability (%)
5	81	11	4	4	0.25	30.2	90
10	85	3	7	5	0.35	6.6	90
13	84	5	7	4	0.16	42.5	95
14	95	4	1	0	0.10	16.0	80
15	67	15	8	10	0.22	6.6	93
18	72	9	8	11	0.11	7.8	80
19	40	21	1	38	0.13	24.0	93
2	67	2	0	31	0.11	24.0	92

nary alveolar proteinosis in 1963. They used a balloon-tipped catheter placed transnasally and positioned fluoroscopically. Subsequently Ramirez found this awkward and offered whole-lung lavage as an alternative [11]. In the same year, Finley and associates [3] developed the technique of selected lobar lavage using a metras catheter with a cuffed tip. Since then, others have used the flexible fiberoptic bronchoscope, with or without an attached balloon at the tip, to lavage the isolated lobe or segment [1, 19].

In this study, three bronchoscopes were used: the Machida FBS-6TL, the Olympus BF-B2, and the Meditech 7S/4.5/70. For this last, the manufacturer cemented a small cuff on the tip of the bronchoscope so that we were able to inflate the cuff and achieve isolated lobar lavage if desired. Using these bronchoscopes, 50% of the lavage fluid was recovered in the volunteers, no difference being apparent between smokers or nonsmokers (see Table 1). The mean age of 30 years and normal pulmonary function tests ruled out significant obstructive disease. This was in contrast to the other two groups. These patients had a long history of smoking, they were older, and 6 had carcinoma of the lung (see Table 2). These groups had mean returns of 35% which are consistent with work done by Finley [3], Thompson [17], and their colleagues showing that lavage returns are much less in patients with chronic obstructive pulmonary disease.

The maximum volume of saline solution used was 300 ml. Studies in humans by Finley and associates [3] indicated that this volume of solution produced minimal transient damage in lungs. Similar work in dogs by Kylstra [8] documented this also.

Lobar lavage had no advantage over sequential segmental lavage. In the conscious patient it seemed to have the disadvantage of displacement of the balloon cuff with coughing. Also, it made the procedure more difficult as well as irritating to the tracheobronchial tree of the patient.

The transient decrease in PaO_2, which returned to normal prebronchoscopy levels in all patients within 4 hours, reflects a ventilation perfusion mismatch. The extent of this decreased PaO_2 was less in the patients who had bronchoscopy under general anesthesia, through an endotracheal tube. The mean decrease was 12 mm Hg (see Table 2). In the group of patients who underwent bronchoscopy transnasally under local anesthesia, there was a wide range in the degree of arterial hypoxemia, ranging from a low change of 21 mm Hg to a high of 140 mm Hg (average fall, 65 mm Hg) (see Table 1).

A Hospitek aerosol mask with flow rates of 6 to 8 liters per minute was used during this study. The inspired oxygen concentration ranged widely during bronchoscopy in each patient, due to positioning of the mask and patient cooperation. Although it is not possible to calculate the exact alveolar-arterial gradient in each patient in the absence of an exact inspired oxygen concentration, the uniform finding of decreased PaO_2 in all patients reflects decreased ventilation in the presence of a preserved blood supply. The two contributing factors for decreased ventilation are alveolar filling by the lavage fluid and bronchoconstriction, which occurs during bronchoscopy. The finding of lesser changes of decreased PaO_2 in the group of patients having bronchoscopy under general anesthesia, through an endotracheal tube, reflects better control of the airway, less coughing, less bronchospasm, and abolition of local reflexes under general anesthesia. All of these factors help the ventilation perfusion relationship.

In contrast to the uniform, although variable, finding of decreased PaO_2 in all patients having bronchoscopy, the effect on alveolar ventilation reflected in the $PaCO_2$ was minimal and statistically insignificant. Our finding of the development of hypoxia in the volunteers during bronchoscopy and lavage reinforces the earlier results of Karetzky and co-workers [7] and emphasizes the value of using supplemental inspired oxygen during bronchoscopy as well as lavage.

There were no complications. The patients had only the minor discomfort of a sore throat after the procedure.

Changes of alveolar filling were present in chest roentgenograms of 25 patients. The changes seemed more prominent the greater the volume used. All patients in whom more than 200 ml of lavage fluid was used and some in whom 200 ml was used showed these changes. Chest roentgenograms made 24 hours later in 5 patients were negative, documenting the transitory nature of the alveolar filling process.

The cells recovered from the lavage fluid showed a preponderance of alveolar macrophages (see Table 3). The numbers of macrophages ranged from 6.6 million to 42.5 million. Smokers had two times more harvestable macrophages than nonsmokers. Macrophage viability averaged 90%. Bronchial epithelial cells were present in some specimens but never represented a majority of the cells.

Mean protein values of lavage fluid in those studied was 0.18 mg per milliliter. Preliminary

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reports from this laboratory showed that macrophages obtained in these studies were able to ingest and kill *Staphylococcus aureus* in both autologous bronchopulmonary lavage fluid and serum [4]. Macrophage antistaphylococcal activity was directly related to the protein content of bronchopulmonary lavage fluid.

These studies indicate that effective segmental and lobar lavage can be done using the flexible fiberoptic bronchoscope with minimal risk to the patient. Macrophages and proteinaceous material from the alveoli can be harvested and studied. We found sequential segmental lavage to be the easiest way to carry out this process. The tip of the bronchoscope is gently wedged in the segmental orifice and irrigation carried out. Then the material is aspirated. Each segment is lavaged successively. Lobar lavage done with the balloon tip was technically more difficult in the conscious patient, and there was no precise control over which segment was being lavaged. In sequential segmental lavage, small volumes of fluid are used, flooding of the lung is avoided, and the risk of damage to the lung is minimized. The average time for the procedure was 45 minutes. Because of its simplicity, specificity, rapidity, and low risk, sequential segmental lavage may be the method of choice in therapeutic as well as diagnostic lavage.

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Surgical Manifestations and Results of Treatment of Pulmonary Coccidioidomycosis

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ABSTRACT **Fifty consecutive patients with pulmonary coccidioidomycosis undergoing operation in an eight-year period were analyzed with regard to clinical and roentgenographic indications, surgical procedure, complications, and recurrence. Surgical indications could be divided into operation necessary primarily for diagnosis (22 out of 50, 44%), and operation because of suspected residual complications of coccidioidomycosis requiring therapy (28 out of 50, 56%). Of 16 patients with solitary nodules, 2 had lobectomy and 14 had wedge resection with no recurrence. Of 24 patients with coccidioidomycosis cavities, 14 underwent lobectomy and 10 had lesser resections, with three recurrences.**

Results indicate that (1) resection for primary pulmonary coccidioidomycosis for both diagnosis and therapy is associated with low perioperative risk, (2) routine administration of amphotericin is not indicated, (3) skin tests, serological study, bronchoscopy, and mediastinoscopy may not be diagnostic, and (4) lobectomy is not necessarily indicated since lesser resections are associated with equally low recurrence and complications rates.

Coccidioides immitis is a dimorphic, saprophytic soil fungus endemic to the southwestern United States. It normally exists in mycelial form with the production of arthrospores. Human infection occurs by the inhalation of these windblown arthrospores and usually produces minimal or no clinical infection. Human infection is completely incidental to the perpetuation of the fungal life cycle. Within tissue, the fungus takes the form of endosporulating spherules, which rupture, mature, and perpetuate the infestation. In the spherule–endospore tissue phase, the disease is not contagious; direct person-to-person transmission does not occur. The immunological response to infection with *Coccidioides immitis* is complex and quite variable, resulting in a spectrum of involvement from asymptomatic seroconversion to disseminated fatal disease.

Coccidioidomycosis may have protean and often unusual presentations and is frequently confused with other infectious or malignant diseases. Because of the frequent inability to make conclusive diagnoses by noninvasive means and the relative unfamiliarity of thoracic surgeons with this disease, this review was undertaken.

Material and Methods

A retrospective study of all patients undergoing operation for pulmonary coccidioidomycosis during an eight-year interval at the University of Arizona Health Sciences Center and the Tucson Veterans Administration Hospital was performed. Only patients with pathologically proved coccidioidomycosis on microscopic examination were included. Data were analyzed with regard to clinical and roentgenographic indications, accuracy of serological diagnosis, surgical procedure, complications, and recurrence. Postoperative follow-up ranged from 10 to 90 months (mean, 40 months) in 50 patients. Patients lost to follow-up before three years following operation were not included. There were 40 male and 10 female patients.

The patient population was divided into two major groups depending on the basic indication for operation. Twenty-two of the 50 patients were placed into the "diagnostic" category; the specific indications were an

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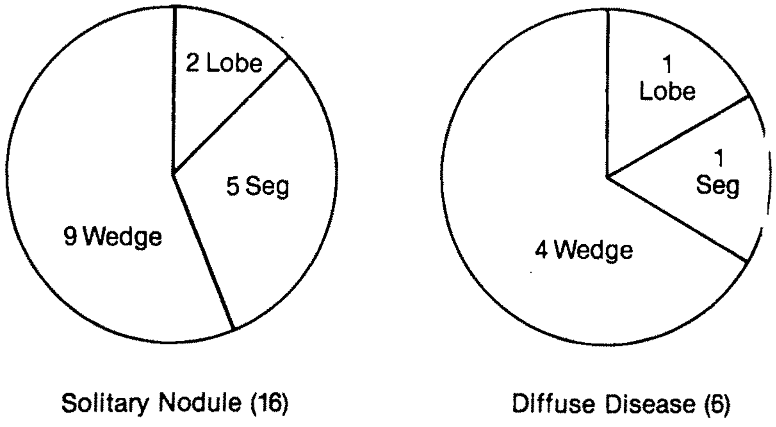

Fig 1. Surgical procedures used in the diagnostic group (22 patients).

asymptomatic solitary nodule in 16 patients and diffuse infiltrative disease in 6. The 28 other patients were categorized in the "therapeutic" group in which the primary diagnosis of pulmonary coccidioidomycosis was either confirmed or strongly suspected. The indications for operation in these patients with residual complications of pulmonary coccidioidomycosis included cavitary disease in 24, pyopneumothorax (secondary to bronchopleural fistula) in 3, and bronchial obstruction in 1 patient.

Preoperative Skin and Serological Testing

DIAGNOSTIC GROUP. In the group of 22 patients undergoing thoracotomy for diagnostic purposes, only 54% (12 patients) had a positive skin test. Of the 16 patients in whom serological (complement fixation) results were available, only 1 (6%) had positive titers.

THERAPEUTIC GROUP. Of the 28 patients in the group undergoing thoracotomy for residual complications of primary pulmonary coccidioidomycosis, 89% (25 patients) had positive skin tests. At the time of operation, 62% (16 patients) of the 26 patients in whom serological results were available had positive complement fixation titers.

Operative Procedure

DIAGNOSTIC GROUP. Sixteen of the 22 patients in this group underwent exploratory thoracotomy for solitary nodules (Fig 1). Nine patients had wedge resection, 5 had segmentectomy, and only 2 had lobectomy. Of the 6 patients undergoing thoracotomy for diffuse infiltrative disease, 4 had wedge resection, 1 had segmental resection, and 1 had lobectomy. All 6 of these patients were immunosuppressed secondary to chemotherapy or leukemia or a combination of these.

THERAPEUTIC GROUP. Of the 28 patients in this group, 24 underwent thoracotomy for cavitary disease. Only 6 of these patients were seen with severe hemoptysis. There were fourteen lobectomies, four wedge resections, and six segmental resections for cavitary disease (Fig 2). Three patients were seen with a pyopneumothorax and bronchopleural fistula secondary to rupture of a coccidioidomycosis cavity into the pleural space. There were two thoracoplasties and one lobectomy performed in this group. One patient was seen with distal tracheal obstruction secondary to an intrabronchial coccidioidomycosis mass lesion requiring bronchoscopic resection.

Results

Complications

For the total group of 50 patients, there was one fatal and one nonfatal complication. A 43-year-old man who underwent a right lower lobectomy for a pyopneumothorax secondary to rupture of an active (positive coccidioidomycosis culture in sputum sample) coccidioidomycosis cavity died of sepsis and a disseminated intravascular coagulopathy one week following operation. There was one reoperation for hemorrhage from a bleeding intercostal artery following lobectomy. There has been no postoperative empyema, bronchopleural fistula, or wound infection. Within a

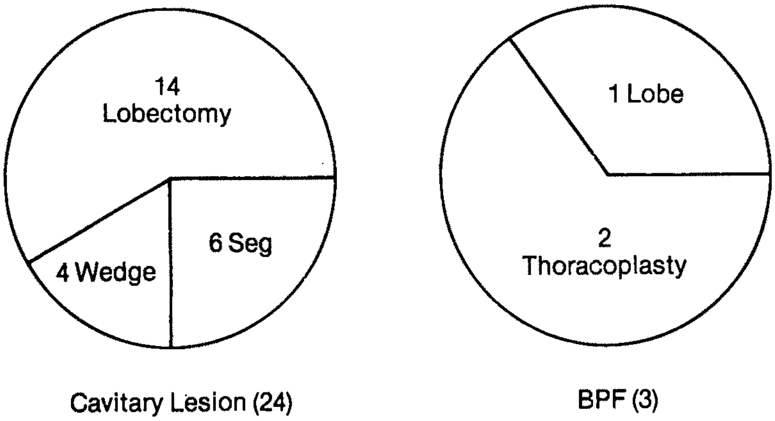

Fig 2. Surgical procedures used in the therapeutic group (28 patients). (BPF = *bronchopleural fistula.)*

month of exploratory thoracotomy, 4 of the 6 immunosuppressed patients died of the primary disease after they began amphotericin B therapy. Amphotericin B was used perioperatively in 11 patients in a total dose ranging from 500 mg to 3.5 gm. It resulted in reversible renal insufficiency in 5 patients.

Recurrences

Three patients, all with cavitary disease, had late recurrence. One patient had recurrent disease in the right upper lobe five years following wedge resection of that lobe. A second patient who had positive sputum cultures for coccidioidomycosis had a recurrent (or residual) coccidioidomycosis cavity in the superior segment of the left lower lobe two years following left upper lobe resection for a similar cavity. This patient had received 3 gm of amphotericin B following the first operation (left upper lobe resection). In another patient, a diabetic who had a left upper lobe segmentectomy, a second focus developed in the right upper lobe several months later and necessitated lobectomy.

Comment

More than half of the patients with pulmonary coccidioidomycosis acquire it asymptomatically, and only a small fraction of those patients infected ever require medical or surgical therapy. Roentgenographic findings are varied, usually showing infiltrates, hilar or mediastinal adenopathy, and pleural effusions in the acute stage. Particularly, but not exclusively, in an immunosuppressed host, the disease may progress rapidly toward dissemination with pulmonary miliary involvement. In 6 patients with underlying malignancies, diffuse infiltrates were revealed on chest roentgenogram and proved to be disseminated pulmonary coccidioidomycosis. All 6 patients were white. Patients on high-dose corticosteroids and other immunosuppressive medications, especially those with lymphoreticular malignancies and organ transplants, are particularly susceptible to dissemination because of altered cell-mediated immunity. These individuals often have negative skin tests and blunted antibody responses to coccidioidomycosis.

Although several other major risk factors predisposing toward coccidioidal dissemination have been identified in addition to immunosuppression, the patient population in the present study did not allow subsequent analysis of these factors. Dark-skinned race, increased age, pregnancy, and female sex have all been cited as statistically significant correlates of dissemination of pulmonary coccidioidomycosis. Our group of 40 male and 10 female patients included only 5 who were not white, none of whom had any complications.

In the more long-term setting, the roentgenographic presentation usually is either a solitary nodule or a persistent cavity of varying size and wall thickness. Probably one of the more widely accepted indications for operation in patients with pulmonary coccidioidomycosis is to confirm the diagnosis and rule out a malignant lesion. Despite evidence to the contrary [2], our data and those of others [2, 3, 7] indicate a significant incidence of false negative results based on skin and serological testing. More important, even when these tests are positive, they do not prove that a given nodule is coccidioidal in origin. Depending on the size and location of a coccidioidomycosis nodule, limited resection (wedge or segmentectomy) with adequate margins grossly (removal of palpable disease) is usually sufficient. This was done in 14 of 16 patients in our series with no complications and no recurrence.

Coccidioidal cavities result from central necrosis of a pneumonic infiltrate. Statistically, serious problems from chronic coccidioidomycosis cavities are not common. The major potential complications are secondary infections (pyogenic or other fungal), rupture resulting in pyopneumothorax, pulmonary hemorrhage, which is rarely severe, and persistent disease with or without positive sputum. No definitive statement can be made regarding a correlation between cavity size and incidence of subsequent complications.

Of the 28 patients undergoing operation for residual complications of pulmonary coccidioidomycosis, cutaneous reactivity to intradermally administered coccidioidin (89%) and detection of complement fixation antibody titers (62%) were much more reliable than in the diagnostic group.

Surgical treatment of cavitary pulmonary coccidioidomycosis remains somewhat controversial with regard to indications and extent of resection. Serious complications are uncommon but do occur [5]. Several early studies [1, 4, 6, 8] showed a rather significant incidence of postoperative complications following resection for cavitary coccidioidomycosis. In our modest series of 50 patients, 24 of whom underwent resection for uncomplicated coccidioidomycosis cavities, there were no complications and two late recurrences. In 1 of these patients, recurrent disease developed following segmental resection and required a completion right upper lobectomy five years later. The other patient had recurrent (more likely residual) disease of the superior segment of the left lower lobe two years following left upper lobectomy. Both patients were white. The only death in the series occurred in a patient in whom a coccidioidomycosis cavity ruptured and a pyopneumothorax developed. He became hyperthermic and hypotensive intraoperatively and died of sepsis and disseminated intravascular coagulopathy a week after operation.

Because of the low incidence of complications and recurrence in our series, we think it is advisable to consider resectional operation for cavitary disease in any patient who is a reasonable surgical risk. The usual criteria for pulmonary operation are age, cardiovascular status, pulmonary function, renal function, and presence of other disease states. The general indications for operation in patients with pulmonary coccidioidomycosis are a solitary nodule in the absence of classic progression, cavitary disease with hemoptysis or persistence, pyopneumothorax (bronchopleural fistula), need for diagnosis in diffuse disease (immunosuppressed patients), and symptomatic mycetoma.

Most authors would agree that resectional operation for cavitary coccidioidomycosis is indicated for any of the complications of cavitary disease: pyopneumothorax with bronchopleural fistula, secondary infection (mycetoma or bacterial), or hemoptysis. In addition, persistence of a cavity of any size for longer than a year reflects an inability of the patient to eradicate the disease and is also an indication for resection even in the absence of complications.

There has been some debate in the literature concerning the efficacy and indications for the use of amphotericin B perioperatively. Its application is limited principally by its toxicity, mainly nephrotoxicity. There is no conclusive data to support widespread use of this agent, and in fact there is much to defend its use only in specific situations. It may be indicated in the prevention or treatment of pulmonary or extrapulmonary dissemination in patients predisposed to this problem, such as those who are immunosuppressed. It is also used when there is persistent coccidioidomycosis pneumonia, bronchopleural fistula, and empyema with positive sputum cultures. Eleven patients in the present series received amphotericin based on these indications. Reversible renal insufficiency developed in 5 of them, and no positive claims could be made regarding the drug's efficacy.

In conclusion, several points concerning the evaluation and surgical treatment of pulmonary coccidioidomycosis should be emphasized. (1) Resection can be accomplished both for diagnosis and therapy with low perioperative risk. (2) The use of amphotericin B should be reserved for individuals with high-risk dissemination. (3) Immunological screening through the use of cutaneous reactivity and serological antibody titers may be suggestive but not diagnostic. (4) Resection for benign disease should be limited to the minimum necessary to safely attain clear margins, each case taken on its own merits. Uninvolved parenchyma should be preserved whenever possible.

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Discussion

DR. EARL J. BAKER (Phoenix, AZ): This presentation gives a good overview of the war between coccidioidomycosis and mankind in the southwestern United States. I have several comments. One concerns classification. I prefer the Arizona Thoracic Society term *residual* for a quiescent lesion and *progressive* for an active lesion. This allows for comparison with other series and, more important, for precise choice of resection procedure. Conservative operation, as noted by Dr. Salomon, in a residual lesion is uneventful. However, an operation involving a progressive lesion must be totally extirpative. The three recurrent lesions in Dr. Salomon's series were associated with inadequate resection.

Another comment concerns skin tests. Their prime value is when they are persistently negative in a patient with a known progressive coccidioidomycosis lesion. In such a case, they portend anergy or immunocompromise and may support a decision for early thorough resection.

Coccidioidomycosis represents an immunological disaster of varying proportion. Insulin diabetes is associated with a fourfold increase in progressive cavitary lesions. It thus tends to spotlight the immunological factors likely to cause complication or death, and thereby increase our knowledge of this most opportunistic fungus infection.

In 9 of 29 surgically treated diabetic patients with progressive coccidioidal lesions, the known compromising factors of male sex, age over 40 years, dark-skinned race, use of steroid, presence of lymphoid disease, and pregnancy were amplified by that of inadequate resection. The last, here numerically the most important, may allow for both local recurrence and also continued systemic immunocompromise. In this same series, the mean total number of such compromising factors when related to final postoperative patient status was as follows: stable, 1.25; complicated, 2.3; and death, 3.2. Computerized axial tomography scans have been quite helpful in these compromised patients because they occasionally reveal unsuspected secondary lesions.

Dr. Salomon, I appreciated reviewing your timely paper. What do you think is the proper treatment for bilateral cavitary disease? Has this disease been a problem in your team's Arizona-based cardiac transplant program?

DR. CECIL C. VAUGHN (Phoenix, AZ): I enjoyed Dr. Salomon's paper very much and will make just a couple of points gleaned over an approximate ten-year experience in treating this disease. Despite the endemic nature of coccidioidomycosis in the Southwest, the incidence of cancer in solitary pulmonary nodules in Phoenix hospitals remains about 25%. This was shown in a study done by a senior member of this organization, Dr. C. Thomas Read, a good many years ago.

I have found that the skin test and other serological tests are rarely helpful in a differential diagnosis of a solitary pulmonary nodule, and rely most heavily on the history and old roentgenograms. Many of the patients have moved to Arizona within the last two or three years and if their history is taken carefully, there often is a time when they had generalized malaise and cough that was ascribed to a nonspecific illness. In those patients requiring operation, the large majority were done to obtain a diagnosis.

Following a routine preoperative workup for a possible cancer of the lung, bronchoscopy is done. This is rarely helpful when there are more peripheral nodules. I then make a horizontal parasternal mediastinotomy incision. In those patients in whom no disease is found in the mediastinum, I examine the solitary nodule by simply opening the anterior pleura and doing a small limited anterior thoracotomy incision. If the disease appears grossly to be carcinoma, usually a lateral thoracotomy is made. In most of my patients a simple wedge resection through a very limited anterior incision can be done, thereby greatly decreasing the morbidity to these patients.

I disagree with Dr. Salomon on the indication for operation for a solitary cavitary lesion present for more than a year. Many of the patients can go for a considerable length of time without difficulty.

DR. JOHN. R. BENFIELD (Duarte, CA): The fine city air of Los Angeles must protect against coccidioidomycosis because I see relatively few patients with this disease, even though I am right next to the endemic area. The indeterminate pulmonary nodule and the question of coccidioidomycosis present an important issue of diagnosis. For example, shortly after a recent dust storm in the Bakersfield area, I saw 2 patients, each of whom had an indeterminate pulmonary nodule. A diagnosis was established for both with needle biopsy. I am not an advocate of using needle biopsies to exclude the possibility of cancer, but I would like to know what are the consequences of needle biopsy in a large series of patients with coccidioidomycosis.

DR. SALOMON: I thank the discussants for their comments and acknowledge Dr. Baker's important contribution to our understanding of the immunological factors important in coccidioidomycosis. In reply to his question, if I have a patient with bilateral cavitary lesions, I certainly recommend staged resection, with bilateral lobectomies if the pulmonary function is adequate. Lesser resections can be performed depending on the extent of disease and overall pulmonary reserve.

With regard to the question concerning cardiac transplants, we have done four heart transplants in Tucson in the last 10 months. We have not yet seen coccidioidomycosis as a complication.

Parenthetically, coccidioidomycosis has not been a tremendous problem in Arizona in terms of the renal transplantation programs. In fact, only selected patients are at high risk, and they happen to be black people more than 60 years old. Other than that, the incidence of coccidioidomycosis in renal transplant patients is quite low, and our immunosuppressant regimen is very similar to that used for patients having a renal transplant.

In reply to Dr. Vaughn's comments, we would approach the problem of a solitary nodule in much the same way.

In answer to Dr. Benfield's question, we have attempted needle biopsy several times. It is easy to do, but the problem arises when the pathologist attempts to make a diagnosis. If you don't get the diagnostic spherules on needle biopsy, it is possible that you missed a carcinoma. Consequently, we feel a little insecure with this method. We will try it, but if it is negative, like anything else in medicine, it doesn't necessarily mean that the diagnosis has been made.

To conclude, my purpose in bringing this topic to the attention of the Society is really to remind thoracic surgeons of the presence of this disease, particularly those living in nonendemic areas. With the increase in travel and the population growth of the Southwest, I think it may become a more important problem in the future.

Aortic Valve Replacement: A 9-Year Experience

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Naythania Jones, M.D., and Willard M. Daggett, M.D.

ABSTRACT **Experience with aortic valve replacement over a 9-year period is reviewed. Hospital mortality was 5.0%, with an additional late mortality of 15.0% during a mean follow-up period of 4.3 years. There was a 7.5% mortality among the 93 patients who were operated on using direct coronary perfusion. There were no early deaths among the 48 patients operated on using cold cardioplegic arrest.**

Paravalvular leaks developed in 20 patients, and 9 had reoperation. There were no early deaths following elective reoperations for prosthetic valve dysfunction, but urgent reoperation was associated with a 40% mortality. Eighty percent of all patients are still alive at a maximum follow-up of 9 years. Eighty-six percent of the survivors who were in New York Heart Association Functional Class III or IV before operation are now in Class I or II. Hypothermic cardioplegic arrest was found to be preferable to coronary perfusion as a method of myocardial protection during aortic valve replacement. Patients with paravalvular leaks who have a history of left ventricular failure prior to aortic valve replacement should be considered candidates for early elective reoperation, owing to the significantly greater mortality associated with urgent reoperation.

Since the introduction nearly two decades ago of replacement prostheses for aortic valve disease, numerous investigators have attempted to identify factors that are useful as predictors of operative risk and long-term survival of patients undergoing aortic valve replacement. Recent reports by most authors show a substantial decrease in overall operative mortality compared with early reports. There is still considerable disagreement, however, regarding the definition of clinical, hemodynamic, and technical factors influencing the outcome of aortic valve replacement.

The past decade has seen numerous technical refinements in the surgical approach to aortic valve disease. Several different prostheses and bioprostheses are in use at the present time. A tremendous body of knowledge has evolved regarding intraoperative protection of the myocardium from injury during the ischemia period that attends aortic valve replacement. Attention has been focused on the particular problems of the patient with coexisting valvular and coronary artery disease and with varying degrees of ventricular dysfunction. This report summarizes a 9-year experience with aortic valve replacement. It emphasizes the impact of patient-related risk factors, operative techniques, and postoperative complications on the ultimate outcome of operation for aortic valve disease.

Material and Methods

Two hundred patients underwent isolated elective replacement of the aortic valve by one surgeon at Massachusetts General Hospital between August, 1968, and March, 1977. These 200 patients constitute the population studied and reported here. Sixteen of these patients had saphenous vein aortocoronary bypass grafts constructed at the time of aortic valve replacement. There were 144 male patients 15 to 78 years old, and 56 women 22 to 80 years old. Overall mean age was 57.6 years.

Preoperative and operative data were obtained by review of the medical record, the cardiac catheterization report, and the operative report. Follow-up data were obtained from records of office visits or by telephone or written communication with the patient or the primary physician. Patients operated on more recently are not included in this review to ensure a minimum postoperative follow-up of a year. Mean follow-up on living patients was 4.3 years since operation (range, 1 year to 9.4 years). Complete follow-up was obtained on 95% of the patients in the series.

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New York Heart Association (NYHA) Functional Classification, based on preoperative evaluation in this hospital, revealed 8 patients (4%) in Class I, 22 patients (11%) in Class II, 74 patients (37%) in Class III, and 96 patients (48%) in Class IV. Preoperative symptoms included angina (51% or 102 patients), congestive heart failure (also 51%), syncope (28% or 56 patients), and systemic emboli (3% or 6 patients).

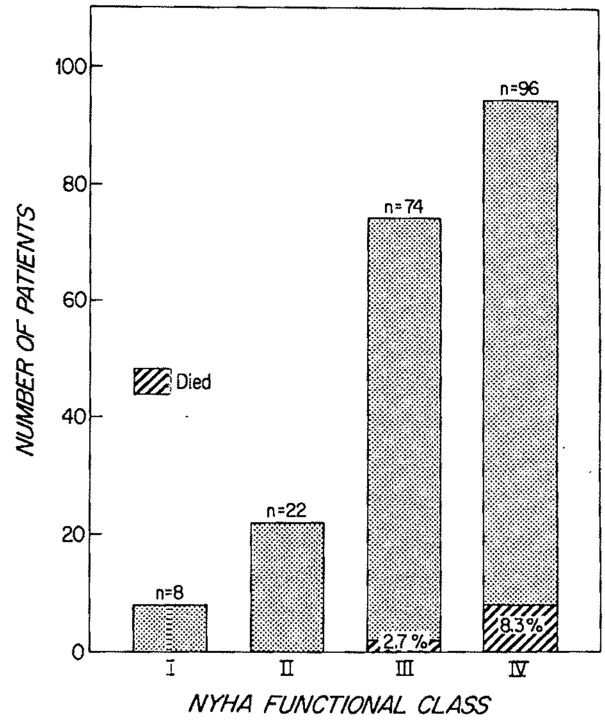
During aortic valve replacement, standard techniques for cardiopulmonary bypass were used. A disc oxygenator was employed prior to 1970, and disposable bubble oxygenators have been used since that time. Early in the series, direct coronary perfusion was used to preserve the myocardium. Subsequently, topical hypothermia was employed. Most recently, cold cardioplegic arrest has been the method of choice for protecting the heart against ischemic injury intraoperatively. Of the 200 valves placed, 182 were Starr-Edwards prostheses, 2 were Björk-Shiley prostheses, and 16 were Hancock glutaraldehyde-stabilized porcine xenografts.

Early death was defined as death prior to discharge from the hospital after valve replacement or, if discharged, death within 30 days of aortic valve replacement. The terms *early death* and *operative mortality* are used interchangeably. Statistical analysis was performed using Fisher's exact or multinomial exact test [11]. For purposes of analysis, the population was divided into two groups. One hundred eighty-four patients underwent aortic valve replacement only and constitute the AVR group. Sixteen patients had concomitant coronary artery bypass grafting and constitute the AVR-CABG group.

Results

Mortality

There were 8 early deaths (4.3%) among the 184 patients in the AVR group, and 2 early deaths (12.5%) among the 16 patients in the AVR-CABG group. The overall hospital mortality for the 200 patients was 5.0%. There were 27 late deaths (14.7%) in the AVR group and 3 late deaths (18.8%) in the AVR-CABG group. The overall mortality during the period of follow-up (mean, 4.3 years) was 15.0%.



Operative mortality by preoperative New York Heart Association (NYHA) *Functional Class.*

Risk Factors

The Figure shows operative mortality according to preoperative NYHA Functional Class. Mortality of Class IV patients is significantly greater than that of the rest of the population (8.3% versus 1.9%, $p = 0.039$).

Preoperative factors potentially related to operative mortality are compared in Table 1. Preoperative diagnoses of pure aortic stenosis and pure aortic insufficiency carried the same operative mortality. As reported previously from this hospital [22], patients with mixed aortic valve disease fared better than those with either pure aortic stenosis or pure aortic insufficiency. In this series, there were no early deaths among patients with mixed aortic valve disease. Overall analysis of mortality by type of valve lesion, however, showed no statistically significant differences. One hundred seven patients with aortic stenosis had aortic valve gradients measured at cardiac catheterization. There were no early deaths among patients with peak systolic gradients less than 70 mm Hg. A 9% mortality was associated with gra-

Table 1. Analysis of Preoperative Factors Potentially Related to Early Deaths after Aortic Valve Replacement

Factors	Patients at Risk	Early Deaths		
		Number	Percent	
Age at operation				
$\leq$ 65 yr	138	3	2.2	$p = 0.024$
> 65 yr (AVR only)	46	5	8.7	
Pure AI	34	2	5.9	$p = 0.669$
Pure AS	144	8	5.6	
Mixed AS/AI	22	0	0	
Aortic valve gradient				
< 70 mm Hg	40	0	0	$p = 0.055$
$\geq$ 70 mm Hg	67	6	9.0	
Aortic valve area				
$\leq 0.7\ cm^2$	53	4	7.5	$p = 0.216$
$> 0.7\ cm^2$	24	0	0	
LVEDP or PCWP				
< 15 mm Hg	89	5	5.6	$p = 0.420$
$\geq$ 15 mm Hg	59	2	3.4	
< 20 mm Hg	114	4	3.5	$p = 0.198$
$\geq$ 20 mm Hg	34	3	8.8	
Pure AS and LVEDP				
< 20 mm Hg	103	5	4.9	$p = 0.108$
$\geq$ 20 mm Hg	19	3	15.8	
Significant CAD	30	4	13.3	$p = 0.330$
No significant CAD	72	6	8.3	

AVR = aortic valve replacement; AI = aortic insufficiency; AS = aortic stenosis; LVEDP = left ventricular end-diastolic pressure; PCWP = pulmonary capillary wedge pressure; CAD = coronary artery disease.

dients of 70 mm Hg or more ($p = 0.055$). Similarly, there were no early deaths among patients with calculated valve areas greater than $0.7\ cm^2$, although the comparison with patients with valve areas less than $0.7\ cm^2$ (early mortality of 7.5%) was not statistically significant. In 148 patients, left ventricular end-diastolic pressure or pulmonary capillary wedge pressure measurements were made preoperatively. Operative mortality was not significantly different for patients in whom either pressure was greater than or equal to 15 mm Hg. Mortality was greater, but not significantly so (8.8% versus 3.5%, $p = 0.198$) among patients with left-sided filling pressure greater than or equal to 20 mm Hg. When only those patients with pure aortic stenosis are considered, a left-sided filling pressure greater than or equal to 20 mm Hg was associated with an operative mortality of 15.8%.

One hundred two patients underwent preoperative coronary angiography. At this center, coronary angiography has been a routine part of the preoperative evaluation of the patient with valvular heart disease since 1973. Thirty patients (29.4% of those examined by angiography) had significant coronary artery disease (70% or greater stenosis of one or more major coronary vessels). The incidence of early death was greater in this group than in patients who were studied and did not have major coronary artery disease (13.3% versus 8.3%). The difference was not statistically significant. The incidence of early death was slightly lower among patients in the AVR-CABG group than among patients with documented coronary artery disease in the AVR group (12.5% versus 14.3%) but again, the groups were small and the difference was not significant.

Operation

Operative factors potentially related to early death are compared in Table 2. Duration of operation and duration of aortic cross-clamp time

Table 2. Analysis of Surgical Factors Potentially Related to Early Deaths after Aortic Valve Replacement

Factor	Patients at Risk	Early Deaths		
		Number	Percent	
Duration of operation (AVR Group)				
≤ 6 hr	86	2	2.3	
> 6 hr	98	6	6.1	
Duration of operation (all patients[a])				
≤ 6 hr	86	2	2.3	
> 6 hr	114	8	7.0	
Duration of CPB (AVR Group)				
0–1 hr	3	0	0	
1–2 hr	114	3	2.6	
2–3 hr	56	1	1.8	
> 3 hr	11	4	36.3	$p = 0.0013$
Duration of CPB (all patients[a])				
0–1 hr	3	0	0	
1–2 hr	115	3	2.6	
2–3 hr	64	1	1.6	
> 3 hr	18	6	33.3	$p = 0.0002$
Duration of cross-clamp (AVR Group)				
≤ 60 min	20	0	0	
60–90 min	102	3	2.9	
> 90 min	61	4	6.6	
Coronary perfusion	93	7	7.5	
Cold potassium cardioplegia	48	0	0	$p = 0.039$

[a] All patients includes those having aortic valve replacement only and those having aortic valve replacement and coronary artery bypass grafting.

AVR = aortic valve replacement; CPB = cardiopulmonary bypass.

did not correlate significantly with mortality. Duration of cardiopulmonary bypass, however, showed a highly significant correlation with early death in the AVR group and in the total population (AVR plus AVR-CABG). A variety of techniques for myocardial preservation were employed. Ninety-three patients (50.5%) had direct coronary perfusion with or without topical hypothermia, with 7 perioperative deaths. Thirty-six patients (19.6%) had topical hypothermia only, with 1 early death. Fifty-three patients (28.8%) had cold ischemic arrest, 48 with potassium cardioplegia, with or without propranolol. Significantly, there were no early deaths in the cold ischemic cardioplegia group ($p = 0.039$).

Postoperative Complications

Seventy-eight patients received postoperative vasopressor support for low cardiac output or ventricular failure. The incidence of early deaths was significantly greater in this group than among patients who did not require such support (6.4% versus 0; $p = 0.014$). Five patients were supported postoperatively with the intraaortic balloon pump for the same indications or for ongoing ischemia. All 5 were successfully weaned from the pump, and there were no early deaths in this group. Eleven patients had substantial intrathoracic bleeding, which necessitated reexploration during the first postoperative day. There were no early or late deaths in this group. There were no major intraoperative neurological complications in the entire series. Eleven patients experienced late postoperative bleeding complications (incidence, 5.8%). All were on a regimen of warfarin anticoagulation. In this group there was 1 death, a result of cerebral hemorrhage. Four patients had late systemic embolic complications.

In 20 patients in the series, a diagnosis of paravalvular leak was made. In some instances, the diagnosis was made on the basis of physical findings (diastolic murmur) with no clinical sequelae; in others, precipitous deterioration required emergency reoperation. A total of 9 patients have had reoperation with repair or replacement of the aortic valve prosthesis. Four of these 9 eventually died. Three other patients with diagnosed paravalvular leaks died. One death occurred 5 years postoperatively and was related to *Staphylococcus aureus* endocarditis. One death was by suicide a year after operation; this patient was in NYHA Functional Class II at the time of death. The cause of the third death was carcinoma of the colon. Hence, there was a 10% incidence of paravalvular leaks. The mortality of patients in this group was 35% (7 out of 20), and the incidence of cardiac-related deaths was 25% (5 out of 20).

Causes of Death

Patients in NYHA Classes III and IV preoperatively accounted for all of the early deaths. Several patients had significant coronary artery disease that was not documented preoperatively by coronary angiography (prior to 1973). There were 4 operating room deaths (patients who could not be successfully separated from cardiopulmonary bypass) and 6 additional in-hospital deaths. Four deaths resulted from myocardial infarction, 2 from ventricular fibrillation, 2 from intractable myocardial failure, and 2 from multisystem failure associated with a low cardiac output state.

Circumstances of late postoperative death are known in most, but not all, cases. Death resulted from myocardial infarction in at least 5 of the 30 patients and from sudden death in 3 patients. Seven deaths were causally related to prosthetic valve dysfunction (paravalvular leak, prosthetic valve endocarditis). Patients in NYHA Functional Class IV preoperatively had a significantly higher late mortality than did the rest of the population (21.6% versus 10.8%; $p = 0.033$). Age greater than 65 years was not a significant predictor of late mortality, though it did correlate significantly with early mortality. Late mortality was greater among patients with aortic insufficiency than among those with aortic stenosis, but the difference was not statistically significant (28.1% versus 14.7%; $p = 0.065$).

Table 3. Rehabilitation after Aortic Valve Replacement

Preop NYHA Functional Class	Postop NYHA Functional Class	No. of Patients
I, II	I, II	19 ++
I, II	III	1 +
III, IV	I, II	102 +++
III	III	9 ++
IV	III	7 +++
IV	IV	1 ++

NYHA = New York Heart Association.

+++ Improved by one class or more	109 (78.4%)
++ Same NYHA class as preop	29 (20.9%)
+ Worse NYHA class than preop	1 (0.7%)
	139 (100.0%)

Rehabilitation

Complete follow-up data were obtained on 174 of the 184 patients in the AVR group (95% follow-up). One hundred thirty-nine patients (80%) were alive at most recent follow-up (mean, 4.3 years). Sixty-eight patients (49%) were in Class I, 53 (38%) in Class II, 17 (12%) in Class III, and 1 (1%) in Class IV. The extent of functional rehabilitation is illustrated in Table 3. One hundred nine patients (78.4%) improved by one class or more compared with their preoperative status. Twenty-nine patients (20.9%) remained in the same NYHA class, and 1 patient deteriorated from Class II preoperatively to Class III postoperatively. The number of patients who improved from Functional Class III or IV preoperatively to Class I or II postoperatively is 102 (73%).

Comment

Retrospective reviews of surgical series that extend over nearly a decade reflect the impact of changing trends in operative management of aortic valve disease. Such is certainly the case with this review of 200 patients having aortic valve replacement. Corroborating the results of larger series [1, 6, 16], risk factors such as advanced age (older than 65 years) and severe functional myocardial impairment (NYHA

Class IV) are identified as useful predictors of operative mortality. More importantly, though, this review highlights the effects of changing trends in aortic valve operation. Three topics in particular appear to merit discussion. They are (1) intraoperative techniques of myocardial preservation, (2) incidence and management of prosthetic valve dysfunction, and (3) surgical management of coexisting aortic valve and coronary artery disease.

Myocardial Preservation during Operation

Protection of the myocardium from ischemic damage during aortic valve replacement has been accomplished using a variety of techniques. Direct coronary arterial perfusion, and subsequently ischemic arrest with topical myocardial hypothermia [9] are the two methods that were in most widespread use during an earlier portion of the past decade. The superiority of normothermic coronary perfusion over normothermic anoxic arrest in terms of hospital mortality and incidence of infarction is well established [12]. There has been, however, considerable disagreement with regard to the choice between direct coronary perfusion and hypothermic ischemic arrest. Proponents of both methods have reported acceptably low hospital mortality. Karp and Lell [10] reported a series of 105 patients having aortic valve replacement without hospital death. Twenty-two patients were operated on using coronary perfusion and 83, using hypothermic ischemic arrest. In 1975, McGoon [13] reported a series of 137 Starr-Edwards aortic valve replacements in which there was only 1 death. Direct coronary perfusion was used. Cukingnan and Carey [7] in 1978 reported a 2.3% hospital mortality for isolated aortic valve replacement and an 11% mortality for combined operations including aortic valve replacement in a group of 121 patients. All these procedures were done with direct coronary perfusion. However, Cohn and associates [5] and Pupello and colleagues [16] reported similarly acceptable results using hypothermic ischemic arrest for myocardial protection.

There are advantages and disadvantages unique to each method. Proponents of direct coronary perfusion cite the protection of the coronary ostia against embolization with calcific valve fragments as a distinct advantage. Buckberg and co-workers [4] stressed the importance of avoiding ventricular fibrillation during coronary perfusion to avoid subendocardial ischemia that results from increased intramyocardial tension during ventricular fibrillation. Mulder and associates [14], from the same institution, reported a small series in which myocardial preservation was accomplished by coronary perfusion with the heart maintained in the beating state. These patients required less postoperative inotropic support than those protected with topical hypothermia or coronary perfusion with ventricular fibrillation. The necessity of maintaining the heart in a beating state is viewed as a technical disadvantage by many and as potentially hazardous if coronary perfusion cannot be maintained with the heart at the warmer temperatures necessary to sustain regular contraction. Fishman [8], Ramsey [17], and their associates described complications of coronary artery cannulation, including arterial dissection and occlusion of the proximal vessel.

Sapsford and associates [21] reported a group of 64 patients undergoing elective aortic valve replacement who were randomly assigned to have either coronary perfusion with mild hypothermia or cold ischemic arrest. The groups were similar in terms of extent of myocardial damage (isoenzyme release) and postoperative cardiac performance, but aortic cross-clamp and cardiopulmonary bypass times were less by 27% and 21%, respectively, when cold ischemic arrest was used.

The present series includes 93 aortic valve replacements with direct coronary perfusion with or without topical hypothermia, 36 aortic valve replacements with topical hypothermia only, and 48 aortic valve replacements with cold ischemic arrest with potassium cardioplegia. Selection of the method of myocardial protection was not by random assignment, but was related sequentially to changing trends in operative management. Potassium cardioplegia was used to achieve and sustain complete electromechanical arrest of the heart. The cardioplegic solution consisted of the following: dextrose, 4 gm/L; sodium bicarbonate, 2 gm/L; potassium chloride, 25 mEq/L; and sodium chloride, 12.64 gm/L. Osmolality was 286 mOsm/L, and pH was 7.8. The results with regard to operative times were similar to those reported by Sapsford and co-workers [21]. Both aortic cross-clamp and cardiopulmonary bypass times were 20% less when cold cardioplegic ischemic arrest was used.

Mortality in the coronary perfusion group was 7.5% (7 patients, including 3 who could not be weaned from cardiopulmonary bypass). There were no deaths in the cardioplegia group. Thus, in our experience, hospital mortality was significantly lower ($p < 0.05$) when cold cardioplegic arrest was employed.

Prosthetic Valve Dysfunction

Difficult decisions regarding the management of patients with prosthetic valve dysfunction must be made with increasing frequency as the population at risk continues to grow. Authors who have focused on this particular problem have classified reoperation after aortic valve replacement in two ways. Parr and his colleagues [15] reviewed 102 patients who underwent replacement of the prosthetic aortic valve and classified these operations as either elective or urgent. They emphasized the significantly lower mortality for elective reoperations than for those performed urgently. In that series, the mortality for elective reoperation was not significantly different from that for primary aortic valve replacement, but the mortality was 42.9% for urgent reoperations. Syracuse and associates [23] reviewed 89 valve reoperations, not limited to the aortic position, and classified patients according to the type of prosthetic valve problem: insufficiency, stenosis, or valve-related systemic disease (infection or hemolysis). They showed that the presence of infection or stenosis was associated with significantly greater mortality at reoperation than was insufficiency (including paraprosthetic leak) without infection. Overall early mortality for aortic valve reoperations was 8%, reflecting the fact that nearly one-half of the reoperations were performed because of insufficiency without infection. Mortality for patients in the high-risk group (infection or stenosis) was 43% and increased to 67% for those undergoing urgent reoperations. (These data include reoperations on prostheses in all positions.)

In the present series, there are 20 patients with a diagnosis of paravalvular leak. This 10% incidence is one-half that reported earlier in 1971 by Shean and colleagues [22] from this institution, presumably reflecting continuing improvement of techniques. Of the 11 patients managed nonoperatively, 1 died suddenly during antibiotic treatment of prosthetic valve endocarditis. Two additional deaths were unrelated to cardiac disease. Nine patients eventually required reoperation. The primary indication for 1 reoperation was coronary artery disease and for another, mitral stenosis with pulmonary hypertension. Suture repair of a small aortic paraprosthetic leak was accomplished in each instance. The 7 additional operations were performed primarily for aortic prosthetic valve dysfunction. All had paravalvular leaks. Of 3 patients with associated infection, 1 died perioperatively. Of the 7 operations necessitated by aortic valve dysfunction, 5 were performed urgently and 2 were elective. There were 2 deaths in the urgent group and none in the elective group. Despite the small size of this group, results in terms of mortality are quite similar to those reported by Parr [15], Syracuse [23], and their co-workers. One major difference is the absence of a greater number of elective reoperations, which may in part be related to the absence from our series of homografts and other ill-fated prostheses, such as the Braunwald-Cutter valve [2] and the early model Beall valve [20]. Of the urgent reoperations, 2 were necessitated by infection and 3 by hemodynamic deterioration with severe left ventricular failure. All 3 of the latter patients had had symptoms of congestive heart failure prior to the initial aortic valve operation. The 2 in whom cardiac catheterization had been performed prior to initial aortic valve replacement had had left ventricular end-diastolic pressures of 22 and 23 mm Hg, respectively.

Elective reoperation after aortic valve replacement can be accomplished with acceptably low mortality. Because of the significantly greater mortality associated with urgent reoperation, patients who develop a paraprosthetic leak and who have a history of poor left ventricular function prior to aortic valve replacement should be considered candidates for early elective reoperation. Patients with no history or evidence of left ventricular failure can be managed conservatively with close follow-up and appropriate antibiotic prophylaxis for dental and other invasive procedures, and of course antibiotic treatment of intercurrent infections.

Coexisting Aortic Valve and Coronary Artery Disease

Authors of several of the largest retrospectively analyzed series of aortic valve replacements have identified coexisting coronary artery disease as both a significant operative risk factor and a leading cause of late deaths [1, 6, 19]. Combined aortic valve replacement and myocardial revascularization has become the treatment of choice for such patients, with significant improvement in long-term survival [18].

In our series of 184 patients who had isolated aortic valve replacement, there were 8 early deaths (see Table 1). In 5 of the 8 who died, postmortem examination revealed significant coronary artery occlusive disease that had gone undocumented or was underestimated before operation. Two deaths resulted from myocardial infarction, 1 from refractory ventricular dysrhythmia and 1 from severe left ventricular failure. Three of the 5 patients had not had preoperative coronary arteriography. Two others had undergone this study, but the extent of coronary artery disease had been underestimated. Two of the 3 patients who were not studied had no history of angina. Our experience differs from that reported by Bonchek and co-workers [3] wherein patients with major coronary obstruction in conjunction with valvular heart disease always had angina pectoris. Accordingly, we disagree with their assertion that coronary angiography can be safely omitted before aortic valve replacement in patients who are free from angina and lack risk factors known to increase the incidence of coronary occlusive disease. Based on our experience, we conclude that all patients more than 40 years old should undergo coronary angiography before aortic valve replacement, even if the history is negative for angina. Likewise, younger patients with significant risk factors for coronary occlusive disease should be considered candidates for angiography as well. Combined aortic valve replacement and myocardial revascularization should be carried out at operation. We agree with Richardson and his associates [18] that hypothermic cardioplegic arrest provides the most myocardial protection during this operation.

In summary, 200 patients underwent elective isolated aortic valve replacement, with concomitant myocardial revascularization in 16. Early mortality was 5.0%, and 80% of all patients were alive at most recent follow-up (maximum follow-up of 9 years; mean follow-up of 4.3 years). Despite the low operative mortality in this and other series, there are several areas of improvement in surgical management of aortic valve disease. It appears that hypothermic cardioplegic arrest provides the best intraoperative myocardial protection. Patients in whom paraprosthetic leaks develop and who have a previous history of poor left ventricular function should be managed aggressively, with early consideration of elective repair. All patients more than 40 years old should undergo coronary arteriography prior to aortic valve replacement. In patients with documented coronary artery disease, myocardial revascularization should be accomplished at the time of valve replacement.

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Clinical Experience with the Smeloff-Cutter Prosthesis: 1- to 12-Year Follow-up

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ABSTRACT **To determine the long-term results of aortic valve replacement with the Smeloff-Cutter prosthesis, the fate of 358 of 459 (78%) consecutive patients was determined 1 to 12 years postoperatively. There were 319 male patients (70%). Mean age at operation was 57 years (range, 15 to 84 years). Aortic stenosis was the dominant lesion in 267 patients (58%) and aortic regurgitation in 133 patients (29%). Fifty-nine patients (13%) had both aortic stenosis and regurgitation. In addition to aortic valve replacement, 93 patients (20%) had coronary artery bypass, 30 (6.5%) had mitral commissurotomy, 23 (5%) had mitral valve replacement, and 41 (9%) had other procedures. Preoperative status by New York Heart Association Functional Class was: Class I, 3 (1%); Class II, 39 (8%); Class III, 148 (32%); and Class IV, 269 (59%). Operative (30-day) mortality was 8.5% (39 out of 459).**

Functional improvement was obtained in all postoperative survivors: 345 (82%), Class I; 63 (15%), Class II; and 12 (3%), Class III. A perivalvular leak developed in 6 patients (1%) and subacute bacterial endocarditis in five (1%). Actuarial long-term survival was 80% at 5 years and 71% at 8 years. Thromboembolism occurred in 34 patients (9.5%). The incidence of thromboembolism per 100 patient-years for patients receiving no anticoagulants was 5.4; antiplatelet agents, 2.9; and Coumadin (sodium warfarin), 2.6. Major thromboembolism was uncommon in patients on a regimen of sodium warfarin but major morbidity from bleeding was significant.

The Smeloff-Cutter prosthesis, introduced in 1964, has been used without further modification in either material or design since September, 1966 [1]. The literature available assessing the long-term results of this prosthesis is scanty compared with that for the Starr-Edwards prosthesis. However, previous reports [1–4] of experience with this valve are encouraging, especially with regard to the low incidence of thromboembolism and the total absence of material failures. This report is based on the experience of two surgeons (G. C. M. and J. F. H.) who performed 459 consecutive aortic valve replacements using the Smeloff-Cutter prosthesis between 1969 and 1977.

Materials and Methods

A retrospective review was made of 459 patients who underwent consecutive aortic valve replacement with a Smeloff-Cutter prosthesis between 1969 and 1977. Follow-up was possible in 358 patients (78%) by letters to the patient and referring physician (290 patients), by telephone (53 patients), or direct follow-up in the clinic (15 patients). Of the 459 patients, 319 (70%) were male and 140 (30%) were female. The mean age at operation was 57 years (range, 15 to 84 years).

Actuarial survival curves were constructed by standard methods [5]. Operative deaths were omitted; patients dying of any cause were included as cardiac deaths. Patients lost to follow-up were withdrawn at the appropriate time.

Aortic valve lesions were designated aortic stenosis or aortic regurgitation or a combination of both according to the criteria described by Hirshfeld and colleagues [6]. Aortic stenosis was defined as severe aortic stenosis with 1+ or less aortic regurgitation; aortic regurgitation was defined as severe aortic regurgitation accompanied by a peak systolic left ventricular outflow gradient of less than 25 mm Hg. The lesion was aortic stenosis in 267 patients (58%) and aortic regurgitation in 133 pa-

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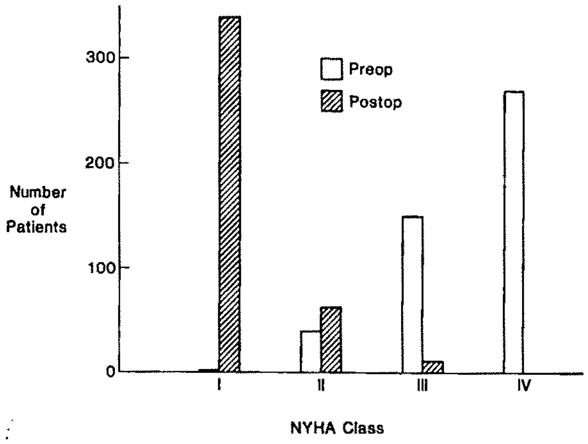

Fig 1. Preoperative and postoperative status by New York Heart Association (NYHA) *Class of 459 patients undergoing aortic valve replacement with the Smeloff-Cutter prosthesis.*

Table 1. Preoperative Symptoms

Symptoms	No. of Patients (N = 459)
Congestive heart failure	217 (47%)
Syncope	34 (7%)
Angina pectoris	81 (18%)
Coronary artery disease present	26 (6%)
Coronary artery disease absent	55 (12%)
Congestive heart failure and angina	60 (13%)
Angina and syncope	24 (5%)
Congestive heart failure and syncope	8 (2%)
Congestive heart failure, angina, and syncope	18 (4%)

tients (29%). Combined lesions with fixed orifice aortic stenosis and aortic regurgitation were present in 59 patients (13%).

The cause of the valvular disease could not be determined in 114 patients (25%). Calcific aortic stenosis accounted for 167 (36%) and rheumatic heart disease, 107 (23%). Annuloectasia with aortic regurgitation and an associated aneurysm of the ascending aorta occurred in 29 patients (6%) and acute or subacute bacterial endocarditis with destruction of the aortic valve and aortic regurgitation, in 12 (3%). Other pathological conditions, including congenital aortic stenosis and thrombosis of a Björk-Shiley prosthesis, accounted for another 30 patients (6.5%).

The preoperative condition of the 459 patients is shown in Figure 1 and Table 1. Of these, 417 (91%) were severely symptomatic and were classified in New York Heart Association (NYHA) Functional Class III or IV before operation. In the whole preoperative group, 303 patients (66%) were treated for congestive heart failure; 183 (40%) had angina pectoris; and 84 (18%) had episodes of syncope. Of the group with angina pectoris, 63 patients had coronary artery disease demonstrable by arteriography while the other 120 had normal coronary arteries.

Thromboembolism was assumed when the clinical episode could have been due to embolism and no other cause was found. Episodes were regarded as major when they resulted in death or permanent disability.

Since bleeding from excessive anticoagulation can cause significant morbidity or even mortality, the incidence of this was calculated in the same way as that of thromboembolism. Bleeding was defined as major when it resulted in death or permanent disability, or required blood transfusion. Minor bleeding was bleeding that required hospital admission. Other episodes of bleeding were regarded as side-effects of Coumadin (sodium warfarin) therapy.

Operative Techniques

In all patients, valve replacement was performed with median sternotomy and normothermic cardiopulmonary bypass utilizing hemodilution priming and membrane oxygenation. The valve was approached through a transverse aortotomy. The coronary arteries were not perfused, and the operation was done under normothermic ischemic arrest with a mean aortic clamp time of 59 minutes (range, 36 to 93 minutes).

Other procedures were combined with aortic valve replacement in 177 patients (39%). Coronary artery bypass using saphenous vein autograft was performed on 93 patients (20%), with an average of 1.1 bypass grafts per patient. Mitral commissurotomy was performed on 30 patients (6.5%) and mitral valve replacement on 23 (5%).

The Smeloff-Cutter aortic valve prosthesis was used when the aortic root and annulus would admit a No. 2 (23 mm) size or larger. If the valve annulus or aortic root was smaller than this, a Björk-Shiley prosthesis was used. The most common size in the series was a No. 3 (198 patients or 43%). The valve was sutured in position with interrupted 2-0 braided Dacron.

Results

Operative Deaths

Thirty-nine (8.5%) of the 459 patients died within 30 days of operation. The cause of 15 operative deaths was pump failure secondary to massive intraoperative infarction. The operative risk was known to be high in 12 of these 15 patients: 10 had triple-vessel coronary artery disease while 2 had refractory congestive cardiac failure. Left ventricular end-diastolic pressure was more than 15 mm Hg in 8 of these patients and was 45 mm Hg in 1. Twelve of them were found to have marked left ventricular hypertrophy at postmortem examination.

Six patients died of noncardiac causes within 30 days of operation. Three bled profusely from a chronic duodenal ulcer; 1 died of acute-on-chronic asthma and 1 of septicemia following valve replacement for acute bacterial endocarditis; and 1 had a fatal cerebrovascular hemorrhage.

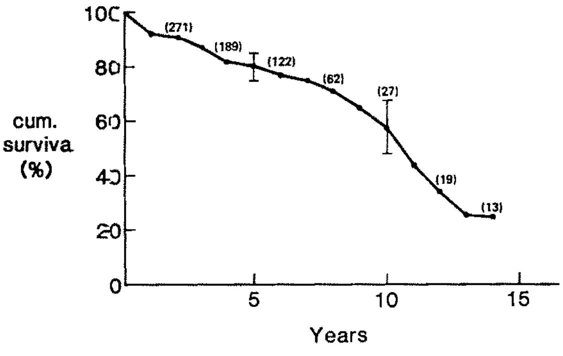

Fig 2. Cumulative survival of 358 patients followed for 1 to 14 years after aortic valve replacement with the Smeloff-Cutter prosthesis. (See text.)

Late Deaths

Sixty-three (15%) of the 420 operative survivors died subsequently of cardiac or unknown causes one month to 12 years after operation. The average mortality for the entire group was 4% per annum. Figure 2 shows the survival curve for the whole group, omitting perioperative deaths, and counting unknown and uncertain causes of death as cardiac in nature. Patient survival at 5 years was 80% and at 10 years, 57%.

Thromboembolism

Thirty-four patients (9.5%) had episodes suggestive of thromboembolism (Table 2). Twenty-

Table 2. Analysis of Thromboembolism and Anticoagulant Complications in Follow-up Group after Aortic Valve Replacement with Smeloff Valve (N = 358)

Anticoagulant	Embolic Episodes (patients)	Bleeding Episodes (patients)	Patient-Years	Emboli per 100 Patient-Years	Emboli + Bleeding per 100 Patient-Years
ALL EPISODES					
Coumadin	26	27	968	2.6	5.5
Aspirin + dipyridamole	4	0	137	2.9	. . .
None	4	0	75	5.4	. . .
MAJOR EPISODES ONLY					
Coumadin	18	21	968	1.9	4.0
Aspirin + dipyridamole	3	0	137	2.2	. . .
None	3	0	75	4.0	. . .

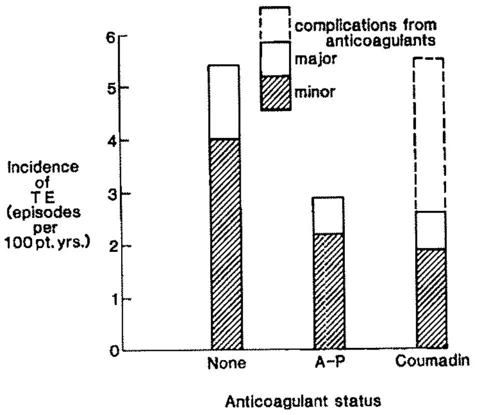

Fig 3. Incidence of thromboembolism (TE) *according to anticoagulant status in 358 patients followed after aortic valve replacement with the Smeloff-Cutter prosthesis. For those receiving no anticoagulant medication, follow-up included 75 patient-years. For those on a regimen of aspirin and Persantine (dipyridamole)* (A-P), *follow-up was 137 patient-years. For those on a regimen of Coumadin (sodium warfarin), follow-up was 968 patient-years. Major bleeding complications from anticoagulant (Coumadin) are added to the incidence of thromboembolism in the last group. (See text and Fig 2.)*

six experienced them while on a regimen of Coumadin; major episodes occurred in 18 patients and a minor episode in 8. Four patients had episodes while on a regimen of aspirin and dipyridamole (Persantine), while 4 patients were receiving no anticoagulants at the time of the embolic event.

The frequency of thromboembolism varied according to anticoagulant status (Fig 3; see Table 2). Patients receiving no anticoagulant had the highest frequency of thromboembolism (5.4 per 100 patient-years). Those on a regimen of Coumadin had the lowest frequency (2.6).

Major emboli were uncommon in patients receiving Coumadin anticoagulation (1.9 major episodes per 100 patient-years). Patients on a regimen of antiplatelet agents or no medication had a similar, but higher incidence of major thromboembolism (2.2 and 4.0 per 100 patient-years, respectively). Overall incidence of thromboembolism was 2.4 per 100 patient-years.

Bleeding from anticoagulant therapy also can have significant morbidity and even mortality. Consequently, the incidence of this was calculated in the same way as that of thromboembolism. These events were also divided into major and minor episodes (see Materials and Methods). Significant bleeding occurred in a total of 27 patients, all of whom were on a regimen of Coumadin. The incidence was 2.9 episodes per 100 patient-years. Major bleeding occurred in 21 patients, an incidence of 2.1 episodes per 100 patient-years.

Improvement in Functional Status

Although 91% (417 out of 459) of the patients were in NYHA Class III or IV preoperatively, 82% (345 out of 420) of the survivors were in Class I postoperatively, with another 15% (63) in Class II. Only 3% (12) had minimal improvement from Class IV to Class III, despite adequate outflow tract and valve size in all these patients (valve sizes ranged from No. 3 to No. 5).

Postoperative Morbidity

Six patients (1%) had perivalvular leaks, which were found from three weeks to 2 years after operation (mean, eight months). In 5 patients (1%), prosthetic subacute bacterial endocarditis developed from six months to 10 years after operation, secondary to infections elsewhere in the body. Two of these patients died of vegetations obstructing normal prosthesis function. Hemolysis was not a clinically significant problem except in 1 patient who had hemolysis secondary to a perivalvular leak. The hemolysis disappeared after repair of the leak. Reoperation was necessary in 8 patients (1.9%) from two months to 8 years after operation (mean, 5.2 years). Five of these patients had perivalvular leaks, and a second valve replacement was necessary in 2 of them to repair the leak. Another 3 patients required a second valve replacement following subacute bacterial endocarditis involving the prosthesis. There were no instances of prosthetic malfunction in this series.

Anticoagulation

Of the 155 patients on a regimen of Coumadin anticoagulation at the time of follow-up, 21 had experienced major bleeding complications of anticoagulants involving either permanent blindness (2 patients), or operation or resuscitation by blood transfusion or both (19 patients). Another 6 patients had minor episodes of bleeding necessitating hospital admission but no operation or transfusion. The 46 patients on a regimen of aspirin and dipyridamole reported no complications from these drugs.

Comment

The Smeloff-Cutter prosthesis is distinctive in several respects. The second model Smeloff-Cutter prosthesis was introduced in September, 1966, and utilizes a mild cure process for the silicone poppet, which is selected for orifice clearance individually for each valve. These steps have virtually eliminated the problem of ball variance [7], which has not been reported in the present model since its introduction. The valve construction includes one piece of titanium without welds, a double-cage, and a full-flow orifice. Both cages are open, and the poppet is smaller than the valve ring when closed, thus allowing minimal retrograde flow and creating a "washing" effect on the valve surfaces.

Long-Term Survival

Actuarial methods [5] provide a better basis for comparison between series than the late mortality quoted in some of them. Several recent series allow comparison on the basis of valve type, long-term survival, and the incidence of thromboembolic episodes. Rubin [8], Oyer [9], and their colleagues, and Bonchek and Starr [10] showed similar improved long-term survival with late model Starr-Edwards prostheses (2310 and 2320) compared with earlier models, achieving 70 to 80% 5-year survival. Operative mortality is omitted from these results. Results with the Björk-Shiley prosthesis were similar [8] and approximated the 80% 5-year survival in the present series (see Fig 2).

The early experience with the Smeloff-Cutter prosthesis of Lee and co-workers [2] and the experience of the Mayo Clinic [11] and New York University [12] using Starr-Edwards prostheses demonstrated significantly lower long-term survival, with a level of 70% 5-year survival. More recently, McHenry and associates [13] reported an improved 5-year survival of 76% with the Smeloff-Cutter prosthesis.

Thromboembolism

The formation of "white" thrombi, consisting largely of platelets, as occurs in cloth-covered prostheses [10], can lead to minor thromboembolism. Major episodes, however, are probably caused by fibrin thrombus forming on the preceding platelet thrombus and subsequent embolism of a mixed thrombus of substantial size. The Smeloff-Cutter prosthesis incorporates a design feature to reduce platelet thrombi—minimal retrograde flow during diastole. Also, the antiplatelet agents aspirin and dipyridamole are administered to reduce platelet thrombi.

Patients receiving no anticoagulant medication had a relatively low incidence of major thromboembolism in this series (4.0 major episodes per 100 patient-years), while patients on a regimen of antiplatelet agents had a significantly lower incidence (2.2 major episodes per 100 patient-years). Patients on a regimen of warfarin seemed well protected from major thromboembolism (1.9 major episodes per 100 patient-years), but major morbidity among those receiving Coumadin occurred with a significant incidence, giving a total major morbidity of 4.0 episodes per 100 patient-years for this group. Those receiving no medication had a higher incidence of minor embolic events, probably reflecting platelet emboli (total of 5.4 episodes per 100 patient-years). For the recent cloth-covered and track model Starr-Edwards prostheses, the incidence of thromboembolism is reported to range from 0 to 7.2 episodes per 100 patient-years in anticoagulated patients [8, 10, 12] to 29 episodes per 100 patient-years in patients whose anticoagulant regimen had been stopped.

In general, tilting-disc prostheses have a higher incidence of thromboembolism than was reported in the present series. The incidence ranges from 0 to 5.0 episodes per 100 patient-years in anticoagulated patients with a Björk-Shiley prosthesis [8, 14]. In addition, thrombosis of the prosthesis with resultant left ventricular outflow tract obstruction remains a problem with the Björk-Shiley and Lillehei-Kaster disc valves [8, 15]. The relatively low incidence of thromboembolism in patients on a regimen of antiplatelet agents only or no medication is a most desirable feature of the Smeloff-Cutter prosthesis, especially in situations of low patient compliance.

In summary, the Smeloff-Cutter valve is a mechanically reliable and durable prosthesis with proved excellent long-term survival and markedly low rates of thromboembolism even in unanticoagulated patients or patients on a regimen of antiplatelet agents only. This prosthesis is probably underutilized, especially in those situations when social factors render follow-up and reliable anticoagulation a difficult and uncertain matter.

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Discussion

DR. EDWARD A. SMELOFF (Sacramento, CA): I thank Dr. David Starr and his colleagues for their careful review of a major series of aortic valve replacements. They bring to our attention the low incidence of thromboembolism regardless of anticoagulant status and provide another look at this situation. They suggest the possibility that the use of Coumadin (sodium warfarin) may not be as desirable as antiplatelet drugs if the complications of bleeding are added to the incidence of thromboembolism.

Our experience covers 15 years—from 1964 through 1979—and 298 individuals having aortic valve replacement and surviving 1,420 patient-years. Only 1 patient maintained on Coumadin has sustained a popliteal thrombus. This patient had a thrombectomy of the popliteal artery preoperatively following heart catheterization. One patient fully anticoagulated died of thrombosis of the valve one month after a thrombosed Starr valve was replaced. One patient had a serious nonfatal cerebrovascular accident when Coumadin was stopped, and 2 patients who discontinued Coumadin abruptly were found at postmortem examination to have thrombosis about the prosthesis. Twelve patients representing 88 patient-years who were never placed on a regimen of Coumadin but were administered aspirin or Persantine (dipyridamole) or both have had no incidence of thromboembolism. In light of these observations, the use of Coumadin with its complications must be reconsidered for patients undergoing aortic valve replacement. Thromboembolism in conjunction with mitral valve replacement remains more significant, seen late as subvalvular fibrosis in 12 of 220 patients. Again, I emphasize that many of these events occurred after discontinuance of Coumadin. Perhaps design changes under study will improve this situation.

When any prosthesis is under discussion, it is interesting to know the causes for and the incidence of its replacement. Although the authors did not include these data, I hope they might comment. In our total experience with 518 replacements since 1964, there have been 39 reoperations. Of 298 patients having aortic valve replacement, 19 were reoperated on, 9 for ball variance before 1966, 1 after 1966 for ball variance secondary to abrasion, 8 for dehiscence, and 1 for bacterial endocarditis. None were operated on for thrombosis. Of 220 patients having mitral valve replacement, 20 were reoperated on, 5 for ball variance before 1966, none for ball variance after 1966, 3 for dehiscence, and 12 with subvalvular fibrosis. Three of these last were children not on a regimen of anticoagulants.

Since ball variance as a problem was eliminated in 1966, dehiscence remains the major cause of reoperation. It is apparent that the defect is primarily in technique rather than with the prosthesis. The technique has improved since we began inserting larger sizes than previously. No valves have required replacement because of structural failure of the prosthesis.

In closing, I thank Drs. Starr, Lawrie, Howell, and Morris for this provocative review of a durable prosthesis that probably can be safely used with antiplatelet drugs alone.

DR. JURO WADA (Tokyo, Japan): I was chairman at Sapporo Medical College Hospital for 23 years. There I had experience with 56 Smeloff-Cutter valves in the aortic position. Five-year actuarial long-term survival was 85%. No anticoagulation was employed.

This result is about 10% better than my experience with 34 Starr-Edwards ball valve aortic implantations. Retrospectively, the Smeloff valve is nonthrombogenic and durable. I think the self-washing mechanism in the design of the Smeloff valve plays a more important role in preventing thromboembolic complications than the materials used in valve design. I incorporated this mechanism in the Wada-Cutter or hingeless valve—origin of the currently popular tilting-disc valve and St. Jude Medical prosthesis.

DR. LAWRIE: We certainly regard it as a privilege to have Dr. Smeloff comment on the use of his valve. Initially, we were attracted to the use of this valve because of two features: the possible hemodynamic benefits of the equatorial ball, and the possibility of a lower rate of thromboembolism due to the open cage and the self-washing mechanism. I think the hemodynamics were perhaps marginally better than those of the comparable non-cloth-covered Starr-Edwards valve but they no longer stand as a major advantage of this valve. However, I think the evidence that we have heard today does suggest that the patient with a Smeloff-Cutter valve who is not on a regimen of anticoagulants is somewhat better off than a similar patient with a non-cloth-covered Starr-Edwards valve and certainly a patient with a cloth-covered Starr-Edwards valve.

I think the patient on aspirin and Persantine (dipyridamole) is reasonably well protected with the Smeloff-Cutter valve, and for us this is pretty much a routine form of protection. Optimal protection will be achieved only with anticoagulation, but we have been discouraged by the morbidity.

We continue to use this valve. We have used it for 12 years, and it is still our primary choice. We have not and still cannot see the advantage in most cases of using a Hancock valve. These valves have a poor orifice to annulus ratio. We now see these major problems in terms of durability in the very patients in whom we need durability most. We have a 15-year durability with only one instance of mechanical failure with the Smeloff-Cutter valve. Dr. Smeloff reported it today. I have always been disappointed in the quality of the sewing ring ever since the aortic Hancock valve was introduced. It seems thin and lacking in padding. We are now hearing reports of an unduly large incidence of periprosthetic leak with the use of this valve.

For all these reasons, we have continued to use the Smeloff-Cutter valve, and I think we have been rewarded by a remarkably low rate of reoperation. This rate is 1 to 2%, and reoperation occurs primarily in patients with a severely calcific aortic valve who required reoperation because of erosion of the annulus.

Over the next few years we have the opportunity to look in more detail at the question of the patient who is receiving no anticoagulants. Baylor College of Medicine is currently operating a full-time cardiac service in the Kingdom of Saudi Arabia. Under frontier conditions, it is not possible to maintain patients on any kind of anticoagulant regimen. Our early experience suggests that these patients do rather better than Western patients who receive no anticoagulants. The somewhat undernourished individuals with a low protein intake appear to have a degree of natural anticoagulation. We have introduced the Smeloff-Cutter valve on this service and so far have been very gratified with the results.

Clinical and Hemodynamic Assessment of the Angell-Shiley Porcine Xenograft

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and Mariano Rico, M.D.

ABSTRACT **Valve replacement with an Angell-Shiley bioprosthesis was accomplished in 449 patients. To evaluate the bioprostheses from this total series, 344 patients who did not undergo associated operation, had no previous operations, or had no other valve substitutes were selected. Hospital mortality was 2.6% for aortic (4 out of 156), 7.2% for mitral (9 out of 125), and 12.7% for multiple-valve replacements (8 out of 63).**

The 323 patients discharged from the hospital were followed for 6 to 36 months. There were 15 late deaths. Hepatitis, bleeding, thromboembolism, endocarditis, and residual valvular incompetence, always periprosthetic, were the major complications.

Forty-five patients with single-valve replacement (16 mitral and 29 aortic) without clinical valve dysfunction were electively recatheterized to assess hemodynamic performance. Measurements were recorded at rest and during exercise on a bicycle ergometer. Functional aortic valve orifice averaged 1.23 ± 0.33 cm^2 and the mean systolic gradient was 21.51 ± 6.68 mm Hg at rest. During exercise, aortic gradient increased to 26.60 ± 7.54 mm Hg and mean functional area to 1.51 ± 0.34 cm^2. In the mitral position, the mean diastolic gradient at rest was 8.44 ± 3.17 mm Hg and the functional orifice area averaged 1.67 ± 0.51 cm^2. Exercise increased the mean gradient to 11.92 ± 3.8 mm Hg and the mean orifice area to 2.05 ± 0.57 cm^2.

Although the tissue valve has become an increasingly popular choice for cardiac valve replacement, experience with the Angell-Shiley glutaraldehyde-fixed porcine xenograft mounted in an anatomical stent is not frequently reported. Early observations of this preparation in laboratory and clinical use and the theoretical advantages of its anatomical Delrin plastic support ring in reducing abnormal stress on the valve tissue encouraged a simultaneous trial at the Cardiovascular Departments of Ciudad Sanitaria Provincial of Madrid and Hospital Universitario of Seville. This report examines the clinical and hemodynamic results observed in the first 449 patients who underwent operation.

Material and Method

Between January, 1977, and June, 1979, 300 patients in Madrid and 149 in Seville underwent single- or multiple-valve replacement with the Angell-Shiley porcine xenograft prosthesis. Of these patients, 105 were excluded from this analysis. These include 26 patients who had associated operations (2, aortic aneurysm resection; 2, ventricular aneurysm resection; 4, pulmonary valve replacement with associated anomalies; 18, aortocoronary bypass graft operation), 69 patients who had undergone previous heart valve operation, and 10 in whom other valve replacement devices were used in addition to an Angell-Shiley xenograft. These procedures would be expected to have some impact on the various valve-related events investigated in this study. There were 197 male and 147 female patients with a mean age of 41.8 years (range, 14 to 68 years).

Table 1 shows the distribution of the 344 patients according to valve replaced and associated valve repaired. It also has the respective hospital mortality. Among the patients who had double-valve replacement, there were 2 with mitral (MVR) and tricuspid valve replacement. Distribution by valve involvement, age, and New York Heart Association (NYHA) Functional Class is shown in Table 2.

At the time of operation, 153 patients (44.5%)

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Table 1. Hospital Mortality According to Valve Replaced among 344 Patients Having Angell-Shiley Xenograft Replacement

Procedure	No. of Patients	Mortality
AVR	130	3 (2.3%)
AVR + mitral or tricuspid repair	26	1 (3.8%)
MVR	75	4 (5.3%)
MVR + tricuspid annuloplasty	50	5 (10%)
Double-valve replacement	41	4 (9.8%)
Double-valve replacement + tricuspid annuloplasty	19	3 (15.8%)
Triple-valve replacement	3	1 (33%)
Total	344	21 (6.1%)

AVR = aortic valve replacement; MVR = mitral valve replacement.

were in atrial fibrillation. Of the 156 patients undergoing isolated aortic valve replacement (AVR), 20 or 12.8% were in fibrillation. Of the 125 undergoing isolated MVR, there were 90 (72%) and of the 63 undergoing multiple-valve repair or replacement, 43 (68.2%) (see Table 2).

All patients in this study were operated on 6 to 36 months ago. In the first half of this period, aortic cross-clamping and valve replacement were combined with myocardial hypothermia induced both by injection of Ringer's lactate solution at 4°C into the aortic root or into the coronary arteries and by continuous irrigation of the pericardial sac with cold saline solution. Subsequently, potassium cardioplegic solution, perfused into the ascending aorta or directly into the coronary arteries, has been used.

Surgical techniques were standardized and had no variation during the period of this review. All the bioprostheses were fixed with interrupted sutures. In the 74 patients in whom a tricuspid annuloplasty was performed, the Carpentier ring was used in 26 and the De Vega method in 48. Carpentier rings were used in the 5 patients in whom mitral reconstruction was associated with AVR.

The size of the 410 valves employed (Figure) tended to be smaller in the patients operated on early in the series. As our experience with the Angell-Shiley bioprostheses increased, we began to use larger valves, especially in the mitral position. At present, we do not use less than a 30 mm valve in the mitral and a 25 mm valve in the aortic position.

Initially our anticoagulation regimen consisted of calcium heparin, 25 mg three times a day administered subcutaneously 24 hours after operation. In 1978, we reduced the early anticoagulation dosage to 25 mg twice a day. Sodium warfarin was administered at the time of removal of the drainage tubes, and calcium heparin was discontinued when the prothrombin time reached 20 to 30%. This range was maintained for 3 months, and the warfarin was gradually discontinued over a three-week period except when the private physician decided to maintain anticoagulation.

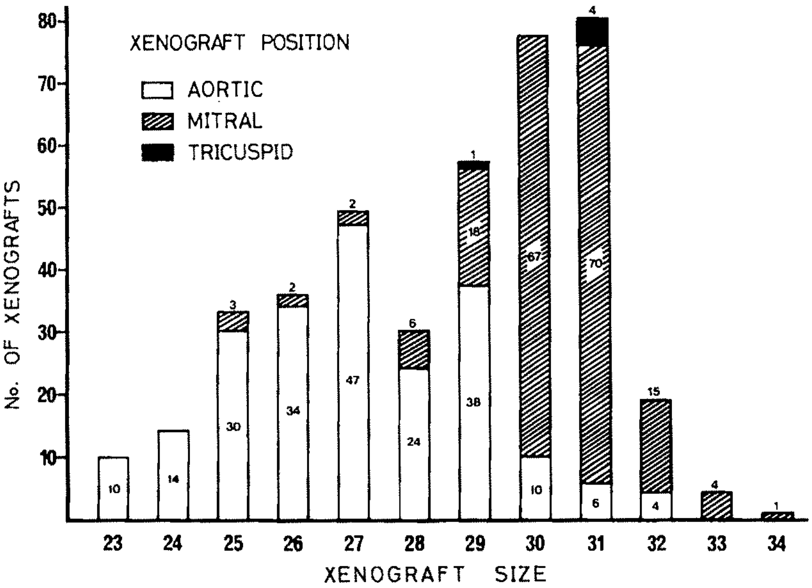
There is a minimum postoperative evaluation of 6 months. Follow-up was obtained in 322 of 323 discharged patients either by examination in the unit or through contact with the patient's private physician every 6 months. Mean follow-up on living patients was 18.5 months (range, 6 to 36 months). We have analyzed overall patient survival as well as the more spe-

Table 2. Patient Data for 344 Patients Having Angell-Shiley Xenograft Valve Replacement

Valve Involved	No. of Patients	NYHA Class (%)				Sex (%)		Mean Age (yr)	Atrial Fibrillation[a] (%)
		I	II	III	IV	M	F		
Aortic	156	11	48	37	4	71	29	42.2	12.8
Mitral	125	1	17	73	9	43	57	42	72
Multiple	63	0	14	73	13	51	49	40.6	68.2
Total	344	5	31	57	7	57	43	41.8	44.4

[a] Percentage of patients in atrial fibrillation at the time of operation.

NYHA = New York Heart Association.



Distribution of 410 Angell-Shiley xenografts according to size and position in 344 patients.

cific criteria of valve performance, including thromboembolic rate, frequency of anticoagulant-associated hemorrhage, and the rate of occurrence of endocarditis. All new episodes of focal neurological defect, either transient or permanent, were considered to be thromboembolic events. Twenty patients who continued to remain symptomatic after the operation or had a clinical diagnosis of valve dysfunction were recatheterized.

To assess the hemodynamic performance of the bioprostheses, 45 patients with single-valve replacement who were asymptomatic and without clinical signs of valve dysfunction were electively reevaluated. Measurements were recorded at rest and during exercise on a bicycle ergometer with the patient supine. Twenty-nine patients with isolated AVR were catheterized through the femoral vessel with simultaneous recording of aortic and transseptal left ventricular pressures. Mean gradients were determined by hand planimetry of five systolic cycles. In 16 patients with isolated MVR, simultaneous left ventricular and left atrial pressures were recorded in the same way. Mean gradients were determined by hand planimetry of five diastolic cycles. Cardiac output was measured by the indicator dilution technique using the average of two separate injections of indocyanin green into the main pulmonary artery and sampled from the central aorta.

Valve areas were calculated by the Gorlin orifice equations. The presence of prosthetic valve or paravalvular incompetence was assessed by aortic and left ventricular cineangiogram. The ejection fraction was calculated by the area length method. Statistical analysis was performed using a Student *t* test.

Results

Hospital Mortality

Hospital mortality was 6.1% (21 patients) in the total series. The causes of death are as follows: low cardiac output, 8 patients; hemorrhage (on a regimen of anticoagulants), 6; neurological deficits, which includes patients with cerebral air embolism, 4; respiratory insufficiency, 1; myocardial infarction, 1; and disseminated intravascular coagulation, 1. Among the 6 patients who died of hemorrhage, 2 had gastric hemorrhage, 2 cerebral, and 2 cardiac tamponade. Only a small percentage of deaths (6 due to hemorrhage and 1 to myocardial infarction) can be considered related to the valve or anticoagulant treatment.

Table 1 shows the hospital mortality with respect to the valve replaced and the associated repair. It is clear that risk is related to the valve involved and the surgical procedure performed. Mortality ranged from 2.3% (3 out of 130) among patients who had isolated AVR to 12.7% (8 out of 63) for those with multiple-valve replacement. Tricuspid insufficiency when associated with mitral disease or both mitral and aortic involvement is a factor that clearly increases patient risk.

Late Mortality

Among the 323 patients discharged from the hospital there have been 15 late deaths (4.6%). Five occurred in patients who had AVR, 6 in those who had MVR; and 4 in those who had multiple-valve replacement. The average age of these patients at the time of operation was 50.7 years for those undergoing single- (aortic or mitral) valve replacement and 28 years for those having multiple-valve replacement. The patients with MVR died 2 to 24 months following operation (mean, 12.1 months); those who had AVR, 4 to 9 months (mean 6.4 months); and those who had multiple-valve replacement, 1 to 8 months (mean, 3.5 months).

Three patients died of congestive heart failure. Three died of acute hepatitis, and 2 died suddenly of unknown cause. Two more died of postoperative cerebral embolism and 2 of cerebral hemorrhage while on a regimen of anticoagulants. One patient died as a consequence of subacute bacterial endocarditis and another of complications of pulmonary insufficiency. One died at reoperation for dehiscence of the bioprosthesis.

The incidence of late death has been as follows: 2.2% per patient-year with AVR; 3.4% per patient-year with MVR; and 4.9% per patient-year with multiple-valve replacement. The general incidence of late mortality (15 patients in 5.803 months of follow-up) has been 3.1% per patient-year.

Hemorrhage

Among the 322 patients followed, 9 have had substantial hemorrhage related to the anticoagulant therapy. Two patients died of cerebral hemorrhage, 1 at forty days and 1 at 9 months after operation. Late cardiac tamponade, retroperitoneal hematoma, and brachial hematoma with radial nerve paralysis were successfully treated surgically. Two episodes of gastric hemorrhage, one of metrorrhagia, and one of serious hematuria were managed medically. The incidence of hemorrhage is 1.9% per patient-year.

Thromboembolism

Among the 322 patients followed, 15 long-term survivors have had embolic episodes: 1 before leaving the hospital, 6 during the 3-month period of anticoagulation, and 9 after withdrawal of warfarin. When these are added to the 2 patients with cerebral embolism in the late death group, the total number of embolic episodes in the series is 18 (11 cerebral, 6 peripheral, and 1 myocardial infarction). Eight of the patients considered as having cerebral embolism have only transient neurological alterations. Of the patients discharged from hospital, 5.6% have sustained episodes of thromboembolism. The overall rate of embolic episodes is 3.7% per patient-year.

Ten of the patients with embolic episodes had MVR (5.6% per patient-year). Five patients who underwent isolated AVR or AVR associated with conservative operation on the mitral or tricuspid valve had thromboembolic complications (2.2% per patient-year). And 3 patients who had multiple-valve replacements had embolism (3.7% per patient-year). Among the 18 patients with embolic episodes, 13 or 72.2% were in atrial fibrillation. Valve thrombosis has not been observed.

Endocarditis

Among the patients in this study, 7 had endocarditis of the Angell-Shiley bioprosthesis within 1 to 24 months after the operation. Four were treated medically with apparent full recovery. All are alive at this writing. One patient has a slight aortic regurgitant murmur, 1 has substantial aortic regurgitation and is scheduled for reoperation, and the third has undergone a second operation for dehiscence of the mitral xenograft apparently not related to the infection. He is well 2 months after the reoperation and 15 months after the original double-valve replacement. The fourth patient is well after 24 months of follow-up.

Two patients had subacute bacterial endocarditis and underwent a second operation. Both are alive and well 13 to 21 months after

Table 3. Data on 8 Patients Who Had Reoperation among 322 Long-Term Survivors

Age (yr), Sex	Preop NYHA Class	Initial Operation	Postop Complication	Interval to Reoperation (mo)	Type of Reoperation	Immediate Result	Long-Term Result: NYHA Class
27, F	II	AVR	Dehiscence	6	AVR	Survived	II
47, F	IV	MVR	Dehiscence	6	MVR	Survived	I
34, M	II	MVR	Endocarditis	3	MVR	Survived	I
47, M	III	MVR	Dehiscence	15	MVR	Died	. . .
45, F	III	MVR + TA	Endocarditis	5	MVR	Survived	II
21, M	III	MVR + TA	Dehiscence	12	Fixation	Survived	I
42, M	III	AVR + MVR	Dehiscence	13	Fixation	Survived	I
24, M	II	AVR + MVR + TA	Dehiscence	8	Fixation	Survived	I

NYHA = New York Heart Association; AVR = aortic valve replacement; MVR = mitral valve replacement; TA = tricuspid annuloplasty.

reoperation and 18 and 24 months after the original valve replacement.

Finally, 1 patient with double-valve replacement died in the acute phase of endocarditis.

The incidence of endocarditis among the patients discharged from hospital has been 2.1%. The total number of patients at risk is 322 during a follow-up period of 483.5 patient-years. The overall incidence of endocarditis is 1.4% per patient-year.

Residual Valvular Incompetence

Among the 322 patients who left the hospital and were followed, 380 valves were at risk, for a total of 6.816 valve-months. There have been 14 valves with residual incompetence, 5 of which had proved bacterial endocarditis. Two of the 5 patients involved were operated on, and a paravalvular leak was closed in both; the valve leaflets were undamaged. After medical control of infection, the third patient was operated on for dehiscence of the mitral xenograft. The fourth patient is scheduled for reoperation. The fifth patient has only slight aortic regurgitation not requiring surgical treatment.

In 9 patients without evidence of infection, incompetence was proved at catheterization to be due to paravalvular leak. In 4 patients it was slight, and in the other 5, paravalvular leak was confirmed at reoperation.

The incidence of residual valvular incompetence has been 2.4% valves per year. No case of mechanical dysfunction of the Angell-Shiley xenograft has been observed.

Reoperation

Reoperations are summarized in Table 3. The postoperative complications warranting a second operation are endocarditis (2 patients) and paravalvular leak (6). All the reoperations were performed by the original team, except that for Patient 94 (Seville), in whom the infected Angell-Shiley bioprosthesis was replaced with a Björk prosthesis in another hospital. The incidence of reoperations has been 1.6% per patient-year.

No case of tissue failure in the xenograft has been observed in these reoperations. It is important to keep in mind, however, that the mean postoperative period for patients having reoperation was only 8.5 months as of this writing.

Late Clinical Status

A comparison between the preoperative and the most recent postoperative evaluation according to the NYHA Classification was made. In the AVR group, the majority (82% or 121 patients) of the long-term survivors were in Class I, 15% (22 patients) were in Class II, and 3% (4 patients) with only 6 months of follow-up and 1 scheduled for reoperation were in Class III. No patient was in Class IV.

In the MVR group, most of the long-term survivors (56% or 62 patients) were in Class I, but an appreciable number (40% or 44) were in Class II. Only 4% (4 patients) were in Class III. No patient was in Class IV.

In the group having multiple-valve replace-

Table 4. Hemodynamic Data in Patients with Angell-Shiley Mitral Valves

Patient No.	Valve Size (mm)	State	Mean Gradient (mm Hg)	Heart Rate (beats/min)	Cardiac Output (L/min)	Calculated Valve Area (cm^2)
1	25	Rest	15.21	110	2.8	0.85
		Exercise	18.50	150	5.5	2.4
2	29	Rest	5.8	60	3.37	1.39
		Exercise	8.8	80	5.45	1.7
3	29	Rest	9.6	98	4.0	1.63
		Exercise	10.7	140	6.0	2.4
4	29	Rest	8.13	158	2.22	0.74
		Exercise	15.42	110	3.0	0.75
5	30	Rest	3.6	80	2.3	1.48
		Exercise	9.08	120	3.8	1.57
6	30	Rest	10.15	106	5.8	2.0
		Exercise	18.2	120	7.8	2.23
7	30	Rest	11.25	104	4.4	1.85
		Exercise	15.22	110	7.1	2.36
8	30	Rest	10.8	80	3.1	1.67
		Exercise	9.6	130	5.2	1.43
9	30	Rest	4.9	86	2.24	1.45
		Exercise	9.4	130	4.0	1.65
10	30	Rest	5.7	64	3.2	1.39
		Exercise	9.7	90	6.5	2.26
11	30	Rest	9.7	80	6.6	2.72
		Exercise	10.1	120	8.5	2.85
12	30	Rest	11.6	74	4.68	1.62
		Exercise	12.4	100	7.52	2.15
13	31	Rest	9.7	79	4.3	1.52
		Exercise	16.5	105	7.98	2.23
14	31	Rest	8.9	80	8.31	2.57
		Exercise	12.9	140	13.4	3.13
15	31	Rest	4.8	60	2.47	1.98
		Exercise	5.9	110	5.18	1.87
16	32	Rest	5.2	74	3.71	1.86
		Exercise	8.16	120	5.71	1.89

ment, 31 patients (62%) were in Class I, 17 (34%) were in Class II, and 12 (4%) were in Class III. No patient was in Class IV.

Thirty-one of the patients had hepatitis early or late after the operation. This high incidence of hepatitis (6.4% per patient-year) has been the cause of late mortality in 3 patients.

Hemodynamic Assessment

The results of the hemodynamic assessment of 16 mitral and 29 Angell-Shiley xenografts are presented in Tables 4 and 5. In the MVR group, cardiac output at rest ranged from 2.22 to 8.31 L/min (mean, 3.96 ± 1.71 L/min) and from 3.0 to 13.4 L/min (mean, 6.4 ± 2.43 L/min) during exercise. The mean heart rate was 80 beats per minute at rest and 117 beats per minute during exercise.

The average mitral valve area at rest was 1.67 ± 0.51 cm^2 for the 16 patients evaluated. Patients with the larger—31 and 32 mm—valves had a greater effective orifice area (1.98 cm^2) than those with 30 mm valves (1.77 cm^2) and those with the smaller 29 mm valves (1.25 cm^2). During exercise, the effective orifice area increased to 2.05 ± 0.57 cm^2 (22.7%).

The average mean mitral valve gradient increased 41% during exercise, from 8.44 ± 3.17 mm Hg to 11.91 ± 3.80 mm Hg. The average exercise-induced gradient for the most frequently used xenograft sizes in the mitral position was 11.64 mm Hg in patients with a 30 mm

Table 5. Hemodynamic Data in Patients with Angell-Shiley Aortic Valves

Patient No.	Valve Size (mm)	State	Mean Gradient (mm Hg)	Heart Rate (beats/min)	Cardiac Output (L/min)	Calculated Valve Area (cm²)
1	23	Rest	17.6	129	4.1	0.85
		Exercise	16	136	7.5	1.63
2	23	Rest	34.28	82	4.13	0.69
		Exercise	24.8	155	10.4	1.51
3	25	Rest	18.46	72[a]	3.9	1.08
		Exercise	37	72	6.3	1.16
4	25	Rest	36.12	69	5.6	0.97
		Exercise	36.6	89	7.0	1.16
5	26	Rest	22.8	69	3.6	1.17
		Exercise	20.9	94	5.25	1.30
6	26	Rest	19.3	80	3.14	0.84
		Exercise	23.21	94	5.49	1.24
7	26	Rest	24	135	4.6	0.79
		Exercise	24.3	164	5.36	0.90
8	26	Rest	24.62	80	6.1	2.0
		Exercise	31.3	120	11.7	2.55
9	26	Rest	40	100	5.5	1.44
		Exercise	40.5	120	6.4	1.62
10	27	Rest	19.35	66	3.7	1.02
		Exercise	24.5	103	5.86	1.07
11	27	Rest	24.28	69	5.6	1.17
		Exercise	38.26	116	10.2	1.40
12	27	Rest	15.6	87	4	1.19
		Exercise	27.2	129	6.3	1.40
13	27	Rest	22.5	80	4.3	0.98
		Exercise	30.6	150	6.3	1.07
14	27	Rest	31.3	101	7.3	1.11
		Exercise	34.08	120	10	1.39
15	28	Rest	14.1	126	4.2	1.17
		Exercise	32.4	140	6.25	1.35
16	28	Rest	23.13	86	6.1	1.32
		Exercise	31	140	10.7	1.54
17	28	Rest	12.2	115	5.8	1.62
		Exercise	11.6	151	8	1.74
18	28	Rest	32	116	7	1.20
		Exercise	37.6	137	9.68	1.58
19	28	Rest	25.7	72	4.9	1.11
		Exercise	28.5	88	7.05	1.46
20	28	Rest	26	80	7.5	2.24
		Exercise	32	120	11.4	2.36
21	29	Rest	28.4	60	6.5	1.62
		Exercise	36.6	80	9.6	1.65
22	29	Rest	14.33	84	3.8	1.07
		Exercise	18.5	114	7.7	1.76
23	29	Rest	14.8	74	3.5	1.02
		Exercise	18.9	104	6.6	1.13
24	29	Rest	10.2	129	4.6	1.39
		Exercise	6.4	130	6.4	1.64
25	29	Rest	16.3	56	4.2	1.60
		Exercise	14	100	5.7	1.80
26	29	Rest	16.27	64	4.05	1.21
		Exercise	23.3	108	9.6	1.83
27	29	Rest	27.8	66	5.05	1.21
		Exercise	24	102	9.5	1.60
28	30	Rest	13.5	95	5	1.39
		Exercise	23.25	138	7	1.48
29	30	Rest	20.6	100	5.2	1.28
		Exercise	24.7	130	8.2	1.67

[a] Pacemaker.

valve and 10.86 mm Hg in patients with a 31 to 32 mm valve.

In the AVR group, cardiac output at rest ranged from 3.14 to 7.5 L/min (mean, 4.93 ± 1.16 L/min) and from 5.25 to 11.7 L/min (mean, 7.84 ± 1.94 L/min) during exercise. The mean heart rate was 87 beats per minute at rest and 118 beats per minute during exercise.

The average aortic valve area at rest was 1.23 ± 0.33 cm^2 for the 29 patients studied, and during exercise it increased to 1.51 ± 0.349 cm^2. The effective orifice area increased 22.7%, a statistically significant difference ($p < 0.05$). There were also differences in the effective orifice area for various valve sizes. The more frequently used sizes of Angell-Shiley xenografts in the aortic position were grouped together for statistical comparison. The larger—29 and 30 mm—valves had a greater effective orifice area (1.31 cm^2) than the medium-sized—27 and 28 mm—valves (1.28 cm^2) and the smaller—25 and 26 mm—valves (1.18 cm^2).

Resting mean aortic gradients averaged 21.51 ± 6.68 mm Hg. In the most frequently used sizes of Angell-Shiley xenograft in the aortic position (see Figure), the mean aortic gradient was 26.46 mm Hg in the 25 and 26 mm valves and decreased to 22.37 mm Hg and 18.02 mm Hg in the 27 and 28 mm and 29 and 30 mm valves, respectively. During exercise, the mean aortic gradient only increased to 26.6 ± 7.54 mm Hg (23.6%).

Comment

Previous reported experience with the Angell-Shiley xenograft has shown it to function well in both the aortic and mitral positions since 1970 [2]. While only 3 of the original patients are in the tenth year of experience, this does support the feasibility of long-term function of the glutaraldehyde-treated xenograft valve. This combined with the theoretical advantages of an anatomically reconstructed bioprosthesis has prompted us to use this device as the valve of choice for single- and multiple-valve replacement since 1977.

Our study establishes that the Angell-Shiley xenograft affords substantial clinical improvement in patients operated on for heart valve disease. Overall, the results compare favorably with those reported with the Hancock and the Carpentier-Edwards porcine xenografts. Our average operative mortality for single-valve replacement is less at 4.6% than the 8.5%* average of reported xenograft series [1]. Approximately one-third of our hospital deaths were related to hemorrhagic problems. By decreasing the early anticoagulation dosage, we have considerably reduced the problem of in-hospital hemorrhage. Our late mortality also has been comparable with the 4.3% per patient-year generally reported for single-valve replacement [1]. Except for the very high incidence of hepatitis, the causes of morbidity are similar to those in other reported series. We have a higher incidence of thromboembolism and hemorrhage than Angell and colleagues [1] reported using the same bioprosthesis. If we compare these data with the first-year incidence of thromboembolism and hemorrhage of other valve series [5–7, 10], there are no substantial differences. The explanation would appear to be due to our short term of follow-up and the higher incidence of embolic events during the early postoperative period [13].

Except for the complications noted, patients have done well clinically even in those instances when valve hemodynamics subsequently were proved to be suboptimal. The improvement in NYHA Functional Class is good, and no patient has returned for primary tissue failure. It is important to note, however, that the longest survivors have less than four years of follow-up. We have no single instance of valve calcification or leaflet perforation, as has been reported (and we have observed) with the Hancock and Carpentier-Edwards valves [1]. In this series it is still too early to provide data relative to the advantages of the anatomical versus nonanatomical method of valve preparation.

Hemodynamic performance is suboptimal and demonstrates increased gradients over those reported with the xenograft by others [4, 9, 11, 12] using the Hancock valve. Angell and associates [1] using the same Angell-Shiley xenograft reported in their small series an average mean aortic gradient that ranged between 16 and 18.7 mm Hg. In contrast, Cevese and co-workers [3] also using the Hancock xenograft reported an average mean aortic gradient of 20 mm Hg in 12 patients, and Rothokopf and colleagues [14] obtained a mean aortic gradient of 23 mm Hg in 9 patients with aortic stenosis. Both these values are similar to the 21.5 mm Hg found in our 29 reevaluated patients with an Angell-Shiley xenograft.

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*The "average" operative late mortality figures were compiled from the data in the tables in reference 1.

In the mitral position, the performance of a single 25 mm valve in our series shows clearly a pattern of mitral stenosis. In the most frequently used mitral valve sizes of 29 to 32 mm, the mean gradients are not noticeably different from those reported by Johnson [8], Cevese [3], and Lurie [11] and their co-workers and are lower than the 11.9 ± 4.57 mm Hg reported by Gallo and associates [6] in a larger series of Hancock xenografts.

In our initial experience with the Angell-Shiley xenograft, smaller valves were used for a given annulus size than in most other series. In view of the substantial transvalvular gradients with the smaller sizes, we consider valves less than 30 mm in the mitral and 25 mm in the aortic position to be inadequate. We now use larger valves for a given annulus size. We find the ability to do this is enhanced by the totally flexible ring, which permits in many instances the use of a valve 2 mm larger than other types of bioprosthesis. While this may require a patch widening of the aorta, we have not resorted to division of the aortic annulus. For MVR, 31 mm and larger valves can be used in virtually every instance.

We will continue with the Angell-Shiley xenograft as our preference for routine valve replacement in the aortic and mitral positions. We will follow closely the comparative incidence of tissue failure, and we anticipate a late decrease in the incidence of thromboembolism and hemorrhage.

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Discussion

DR. WILLIAM ANGELL (San Jose, CA): Dr. Rivera and Dr. Infantes and their colleagues in Madrid and Seville in collaboration with the group from the Montreal Heart Institute are to be congratulated for undertaking this precise study of the results, complications, and hemodynamic performance of a new valve replacement device. Congratulations are particularly in order because, as our recent summarization of the reported valve series in the English literature reveals, only six of the reporting groups, and this includes Drs. Rivera and Infantes, have presented an analysis both of the clinical results and of the valve's hemodynamic performance. In addition, in only two of these six groups has the author been other than the founder or proponent of the particular valve device analyzed. My point is that compiling the literature and analyzing and assessing the data relative to the clinical results and performance of valve devices are extremely difficult even in our modern enlightened age.

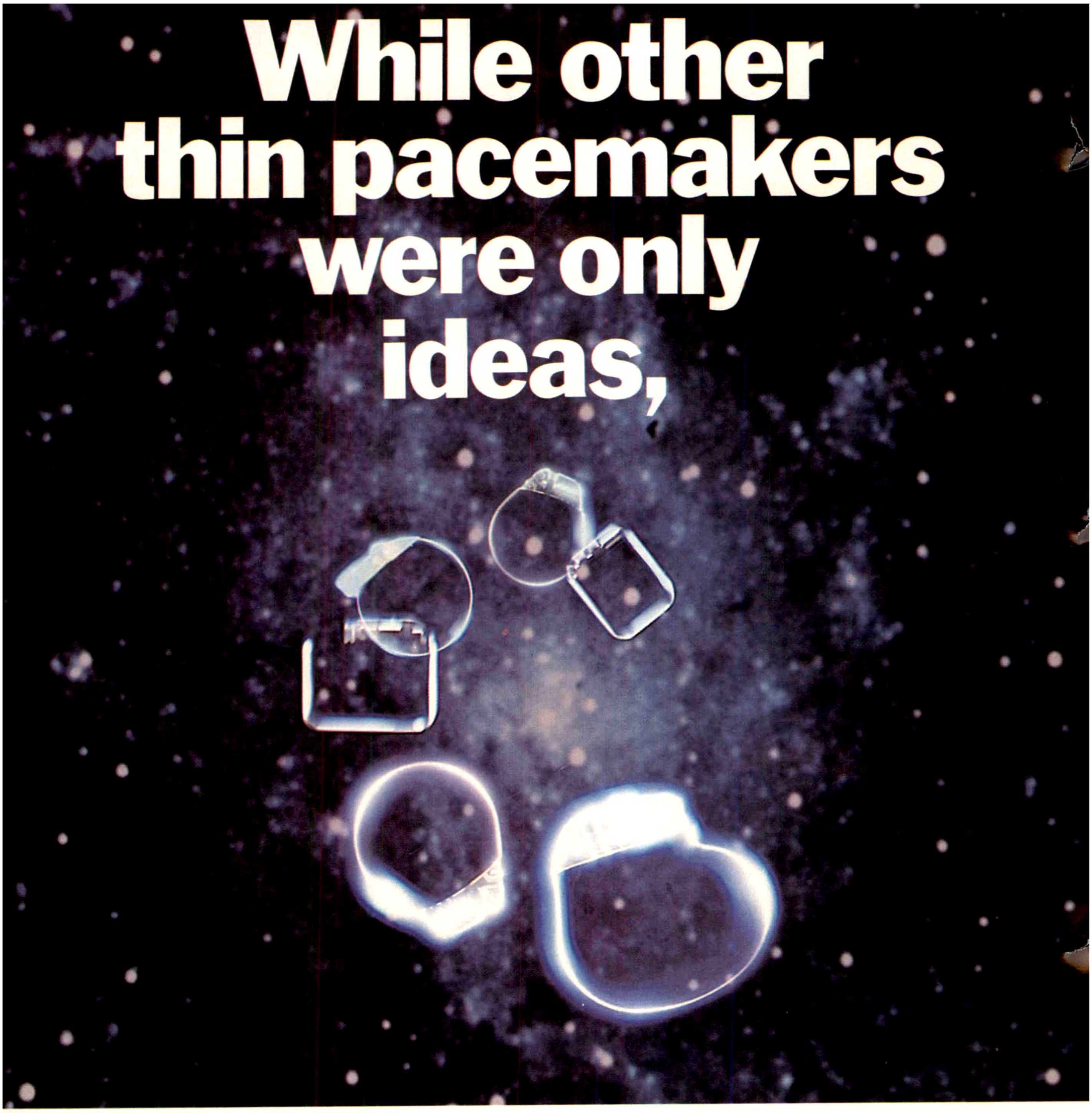
I am obviously prejudiced in favor of the valve being discussed. It is unfortunate that it will not be available commercially in the future due to technical production problems and the related financial margins encountered by the manufacturing company. I use the word *unfortunate* because we have been pleased with the results of our experience as well as that of Drs. Rivera and Infantes. We have about 900 patients that we have been following, and those with the longest follow-up are now in their tenth year. Four of the original group of 6 patients who were operated on in 1970 are doing well with this biological valve and have no evidence of valve dysfunction or deterioration. The other 2 patients died of nonvalve-related causes and without evidence of valve failure in the fifth year of follow-up.

Another point is that the new prototypes of the porcine xenograft that we have been evaluating in the research laboratory look promising. We believe that these valves are more flexible and hemodynamically improved. In fact, in vitro tests would suggest that their performance is at least equivalent to that obtainable with the mechanical prosthesis. Like you, we are left with the dilemma of which valve to select, and I personally have no good answer.

The solution to the problem of tissue valves, I believe, is related to solving the problem of tissue deterioration. Scanning electron photomicrographs show the delamination or separation of the tissue layers within the substance of the glutaraldehyde-treated valve leaflet whereas the normal valve, which is much less impervious to host invasion, has a compact and greater structural integrity.

Over the next several years the answers to the problems with the tissue valve will be forthcoming, and I am encouraged by the ongoing research and development, which will continue to add a great deal to our knowledge in this area.

DR. RIVERA: I thank Dr. Angell for his comments. Whether or not the anatomical method of valve preparation has advantages of durability compared with the nonanatomical one remains to be demonstrated. We will continue to follow closely the incidence of tissue failure in this series of patients with this xenograft.



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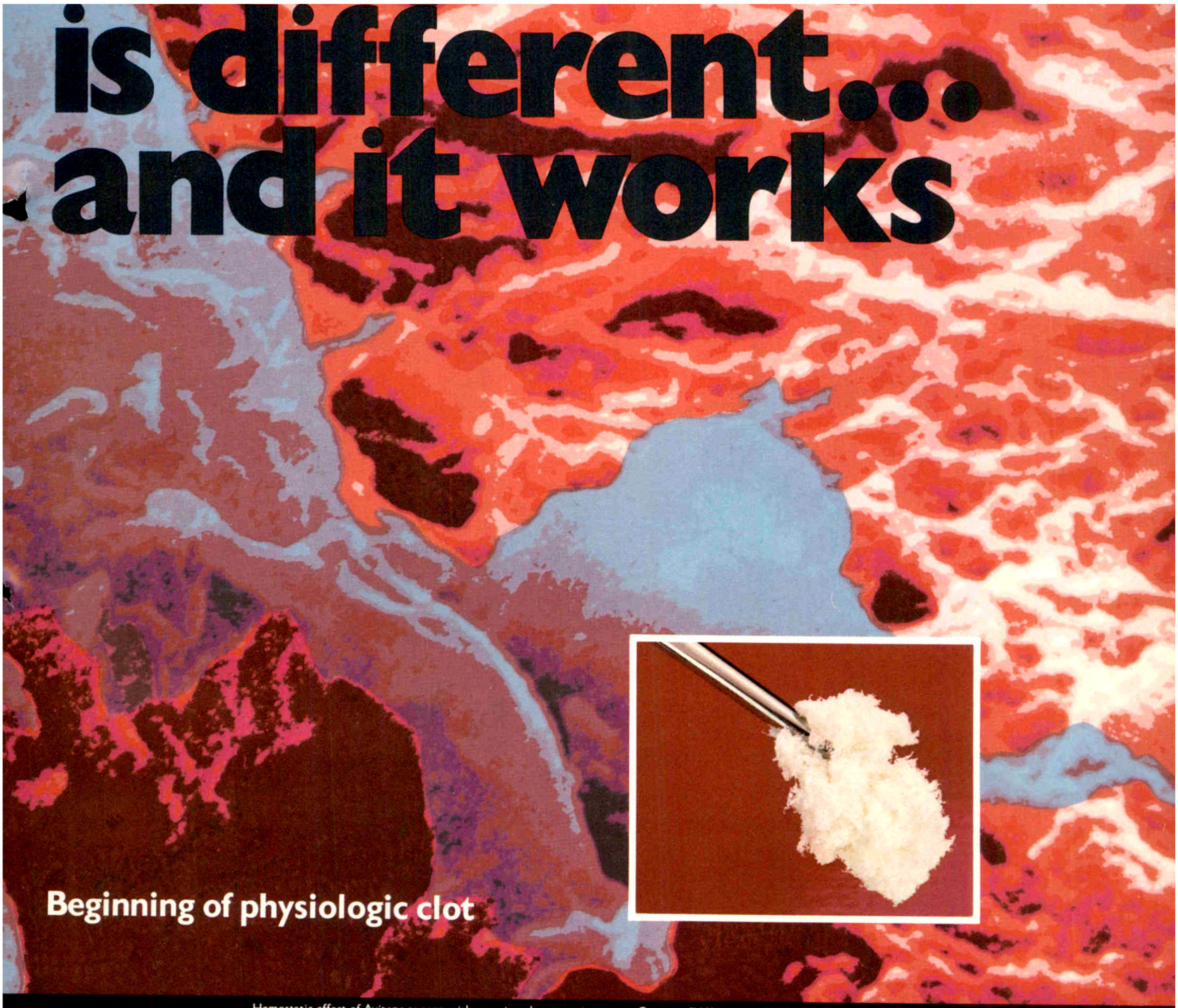

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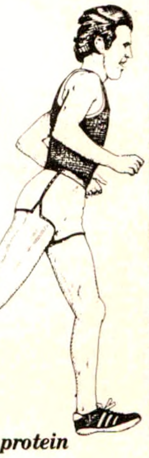

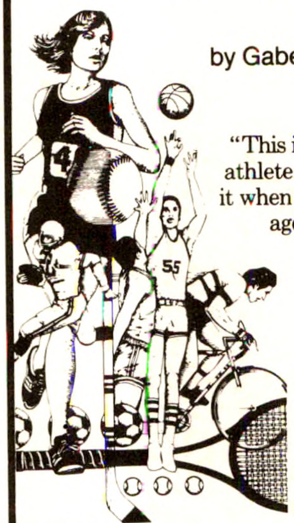

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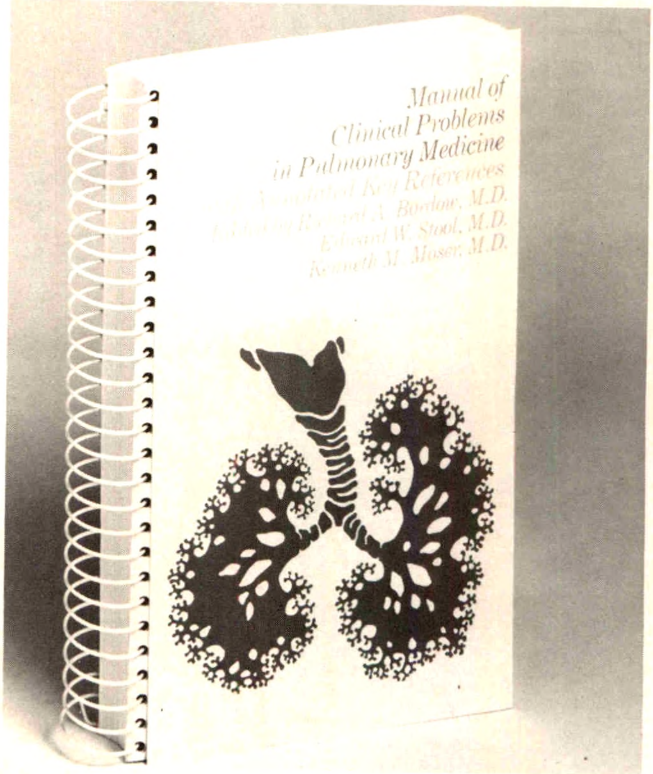

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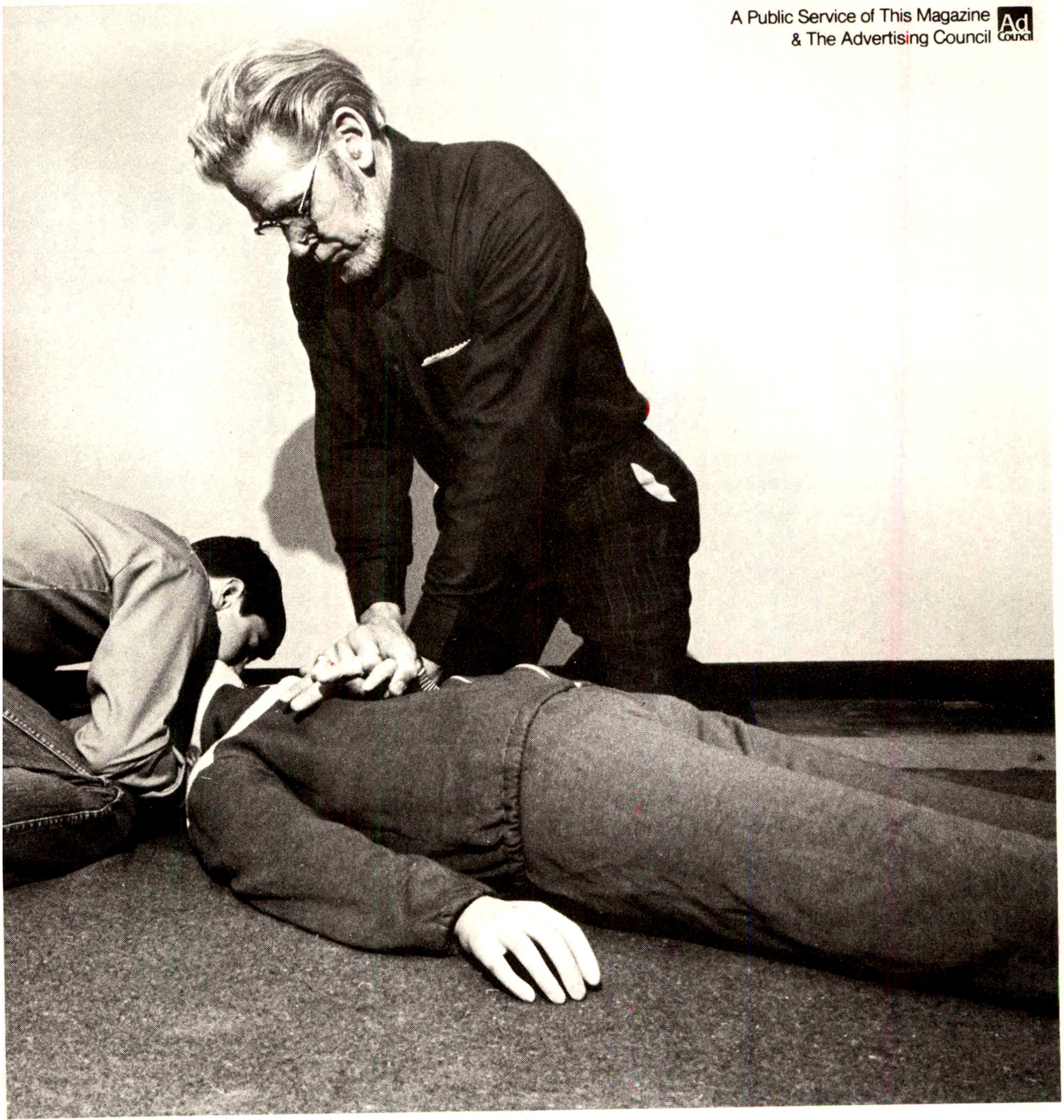

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Pericardial Window for Malignant Pericardial Effusion

John R. Hankins, M.D., John R. Satterfield, M.D., Joseph Aisner, M.D.,
Peter H. Wiernik, M.D., and Joseph S. McLaughlin, M.D.

ABSTRACT **Seventeen patients with malignant pericardial effusion were treated by the creation of a pericardial window. This was done through a subxiphoid approach in 13 patients and through limited anterior thoracotomy or sternotomy incisions in 4.**

There were no deaths and no major complications attributable to the operation. In all patients, relief of the cardiac compression caused by the effusion was immediate and complete. No patient showed a clinically significant recurrence of the effusion, although 1 patient who had received irradiation required pericardiectomy for constriction 5 months later.

Survival was determined principally by the extent of the primary malignancy. Six patients died of the primary tumors within 30 days, but 6 survived 3 to 12 months and 2 are alive at 8 and 21 months.

It is concluded that creation of a pericardial window, preferably by the subxiphoid approach, is the treatment of choice for malignant pericardial effusion. The procedure provides an accurate diagnosis, carries virtually no mortality or morbidity, and affords immediate and long-lasting relief of cardiac compression.

In postmortem studies of patients with malignancy, the incidence of metastases to the heart or pericardium has ranged from 2 to 21% [3, 6]. The effusion that results can cause fatal cardiac tamponade in a patient whose useful life might otherwise be extended by chemotherapy or radiotherapy.

The ideal treatment should ensure complete removal of the effusion and prevent its reaccumulation, with a minimum of discomfort to the patient. Radiation therapy or pericardiocentesis with intracavitary instillation of chemotherapeutic, radioactive, or irritating agents has been advocated by several authors [2, 4, 11–13, 15], with mostly indifferent results. Six years ago, having become dissatisfied with other methods of treatment, we instituted a policy of open surgical drainage, usually by the subxiphoid route, for all patients with symptomatic malignant pericardial effusion. This report presents our experience with 17 patients so treated.

Material and Methods

Sixteen of the patients were adults ranging from 19 to 74 years old. Twelve were men and 4 were women. The remaining patient was a 4-year-old child with Wilms' tumor. The primary malignancies that led to the effusion are as follows: carcinoma of the lung, 12 patients (3 with small cell and 9 with other cell types); Hodgkin's disease, 3 patients; carcinoma of the breast, 1 patient; and Wilms' tumor, 1. All patients had extensive metastatic disease. In no patient was the pericardium the only site of metastasis. In 6 patients, the pericardial effusion was a finding on admission before the patients had received any treatment. In the remaining patients, the effusion occurred during or following treatment with radiation therapy or chemotherapy or both.

Three patients had no symptoms or physical findings of pericardial effusion. All of the remaining 14 patients had varying degrees of tamponade as evidenced by dyspnea, elevated jugular or central venous pressure, and pulsus paradoxus. In 3 patients, the tamponade was severe enough to produce hypotension and oliguria. Echocardiography was employed in 14 of the 17 patients and confirmed the presence of the effusion in each.

In 3 patients, the excision of the pericardial window was performed through a limited left anterior thoracotomy so that suspected lesions in the lung or pleura could also be inspected or biopsied. In the child with Wilms' tumor, the window was created through a median ster-

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Presented at the Sixteenth Annual Meeting of The Society of Thoracic Surgeons, Jan 21–23, 1980, Atlanta, GA.

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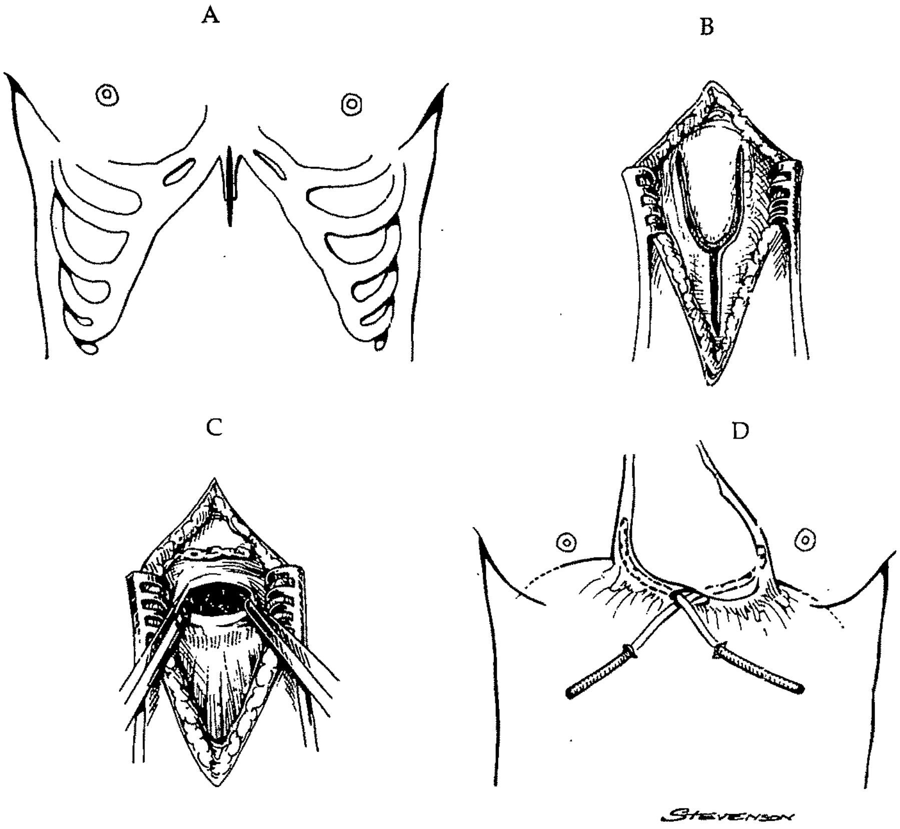

Technique for creation of a pericardial window. (A) The skin incision. (B) The xiphoid process is freed by sharp dissection. (C) The xiphoid process has been removed and the pericardium exposed just cephalad to its junction with the diaphragm. The pericardium is grasped with clamps and gently pulled downward, and a window is created. (D) Drainage tubes have been placed on either side of the heart and are led out through the pericardial window and through stab wounds on either side of the skin incision.

notomy, performed for mediastinal exploration. In the remaining 13 patients, the pericardial window was created through a subxiphoid approach.

When the subxiphoid approach was used, the procedure was carried out under local anesthesia with an anesthesiologist standing by to administer oxygen and sedation, intravenously, as needed. A vertical midline incision 8 to 10 cm in length was made over the lower sternum, xiphoid process, and upper abdomen (Figure). The xiphoid process was freed from its fascial and muscular attachments and then excised. The junction of the pericardium and the diaphragm was located by inspection and palpation. The pericardium just cephalad to this junction was grasped with Allis clamps and gently pulled downward. An incision was made in the pericardium between the two clamps, and then this was extended to include excision of a square or rectangular window of pericardium measuring at least 2 cm in each diameter.

After all fluid was evacuated, the pericardium was explored with the examining finger, and any tumor nodules lying within reach of the pericardiotomy were biopsied. A suction catheter was passed gently around the heart into all recesses of the pericardial sac to make sure all collections of fluid were removed. The pericardial sac was drained with two 24F plastic catheters. One was placed just caudad and posterior to the apex of the heart and the other, lateral to the right atrium. Both were brought out through the pericardial window just created and then through stab wounds in the abdominal wall on either side of the midline incision. Both were connected to waterseal drainage systems to which suction was applied.

The excised window of pericardium was sent to the Pathology Department for gross and microscopic examination. Samples of the pericardial fluid were sent for cytological and bacteriological studies.

The pericardial drainage tubes were removed when the drainage from each decreased to 50 ml or less per day. This usually occurred 48 to 72 hours after operation. In no patient was any agent instilled through the tubes to promote adhesions.

Postoperatively, 7 patients received radiation therapy to the mediastinum and pericardial area. One of them also received systemic chemotherapy. Five others received systemic chemotherapy alone or combined with radiotherapy for their primary malignancies, without specific attention to the pericardial disease.

Results

The amount of pericardial fluid removed was recorded in 16 patients. It ranged from 90 to 1,400 ml, with a median amount of 400 ml and an average of 560 ml. The pericardial fluid in the 16 patients in whom it was described was serous in 2, serosanguineous in 6, and bloody in 8. Tumor nodules or infiltration in the heart or pericardium were observed or palpated in 9 patients. In all 9, histological confirmation of the presence of neoplasm in or contiguous with the pericardium was obtained. A cytological examination of the fluid was not obtained in 5 patients in whom gross tumor was visible or palpable. Among the 12 patients whose fluid was submitted for cytological study, the examination was confirmatory or strongly suggestive of malignancy in 4 patients in whom the surgical specimen or biopsy was also positive. The cytological examination also was positive in 5 patients whose biopsies were negative for tumor. In 3 patients, the biopsy and cytological study were both negative for malignancy. In 1 of them, carcinoma was found histologically in the larger specimen of pericardium that was submitted at the time of pericardiectomy 5 months later. In another, at postmortem examination, carcinoma was found to be invading the right atrium. In the third patient, the postmortem examination showed carcinoma in the lung and peribronchial lymph nodes but none in the pericardium. This was the only patient in whom a malignant cause for the effusion remained unproved.

There were no deaths attributable to the pericardial window procedure. The only complication was a right pneumothorax, which resolved promptly after the insertion of a chest tube.

In all patients the relief of the cardiac compression afforded by the pericardial window was immediate and complete. No patient showed a clinically significant recurrence of the effusion. Eleven patients underwent echocardiography at varying intervals following operation. In 5, the study suggested the presence of a recurrent effusion. Postmortem examination later was done in 2 of the 5, and in neither was the presence of a pericardial effusion confirmed. A third patient is still living 21 months postoperatively and has no symptoms of cardiac compression. One patient who had received irradiation to the chest wall for breast carcinoma was relatively free from symptoms for 4 months but then signs of cardiac constriction developed. A pericardiectomy was required. The thickened pericardium that was removed was infiltrated by carcinoma but the nature of the fibrous reaction suggested that the radiation therapy had also played a part.

Six patients died of progression or complications of the primary tumors within 30 days. Three patients survived for 1 to 3 months, 4 for 3 to 11 months, and 2 for 12 months. Two patients are alive at 8 and 21 months, respectively.

The principal factors determining length of survival were the aggressiveness of the primary malignancy, its stage at the time the pericardial window was created, and the availability of effective chemotherapy or radiotherapy. Thus, the 3 patients with small cell carcinoma of the lung had already received extensive chemotherapy and failed to respond, and all 3 died within 1.8 months. On the other hand, of the 9 patients with non–small cell carcinoma of the lung, 6 survived 1.5 months or more, 1 survived 12 months, and 1 is alive at 8 months. Two of the 3 patients with Hodgkin's disease survived

12 months or more, 1 of whom is alive at 21 months.

Comment

The incidence of metastasis to the heart and pericardium depends largely on tumor type [2, 3]. The primary tumors most frequently giving rise to such metastases are carcinomas of the breast and lung, lymphomas, and malignant melanomas, in that order [3]. In this respect, the present series differs from most reported series in that there were 12 patients with lung carcinoma and only 1 with breast carcinoma. This relative incidence of the two types of carcinoma may reflect patterns of patient referral to this institution based on special research interests that exist here.

The time-honored method of treatment for malignant pericardial effusion has been external radiation therapy to the pericardium [2, 11, 15, 16]. This method is likely to be effective only if the neoplasm is radiosensitive, as in the case of lymphomas [16], and no previous radiation therapy has been administered to the mediastinum. Cham and associates [2], in treating a series of 38 patients with the usual distribution of primary neoplasms, achieved clinical improvement in only 60%. Only 2 of 7 patients with lung carcinoma were improved.

Methods involving pericardiocentesis with the instillation of various antineoplastic or irritating agents have been advocated. A disadvantage common to all such methods is the small but very real risk of fatal needle injury to the heart. Intracavitary gold 198 has been employed infrequently, with a response being achieved only rarely [11]. Intrapericardial radioactive chromic phosphate has also been tried [7, 12, 13, 15]. Because this substance is a beta emitter, it is likely to be effective only in situations in which the tumor burden is small and the histology radiosensitive [4]. Martini and colleagues [12] administered this agent intrapericardially in 28 patients, but recurrent effusion developed in 8 and further therapy was required. Intracavitary instillation of antimetabolites and alkylating agents has been advocated [11, 16]. The results are difficult to assess because of the small number of reported patients and the paucity of data in some of them. These agents have the disadvantage of causing a reactive effusion that can reduce cardiac output further. They also can produce cardiac irregularities and bone marrow toxicity [4, 11]. Davis and colleagues [4] treated 6 patients with tetracycline given through an indwelling pericardial cannula. Three to eight separate instillations were required, and these caused fever and pain. Although all 6 patients were relieved of tamponade and showed no clinical symptoms of recurrence, the period from instillation to death was 112 days or less in 3 patients.

Various surgical approaches have been utilized to treat malignant pericardial effusion. Iturrino and Holland [8] treated a patient with malignant effusion due to metastatic bronchogenic carcinoma by radical pericardiectomy. The patient died of uncontrollable arrhythmia 19 days postoperatively. This operation is far too extensive for the type of debilitated, near end-stage patients who constitute most reported series, including our own. If radical pericardiectomy had been used in the present series, the operative mortality and morbidity unquestionably would have been great and it is doubtful if the relief of tamponade would have been any more complete or long lasting, except in perhaps two instances.

Williams and Soutter [17] created a pleuropericardial window through a left anterior thoracotomy. The edge of the lung was sutured to the edge of the pericardial opening so as to form a dead space in the pleura outside the window. They attempted the procedure in 6 patients with malignant effusion and were successful in 5. One of the 5 died 3 days postoperatively, leaving 4 who benefited from the procedure. One of these required three window operations because the tamponade recurred. Hill and Cohen [7] attempted a similar procedure in 4 patients and were successful in 3. All 3 experienced relief of tamponade but 1 died of recurrent tamponade 13 months later. The pleuropericardial window operation has the disadvantage of requiring general anesthesia and a thoracotomy. A somewhat similar procedure was employed in 3 patients in the present series because they had lesions in the left lung or pleura that required biopsy. Whereas a larger window of pericardium can be excised through an anterior thoracotomy approach, we consider this advantage is outweighed by the need for general anesthesia.

Drainage of the pericardium through the subxiphoid approach was advocated by Larrey [10] in 1829. The method has since been used by others [1, 5, 9, 14] for various types of pericardial effusion, including that due to malignancy. Lajos and co-workers [9] employed the subxiphoid approach in 15 patients with malignant effusion and experienced no recurrences. However, they instilled chemotherapeutic agents into the pericardium through the drainage tubes. Earlier, Goldman and Pearson [6] had performed talc poudrage through a right anterior thoracotomy. We did not administer chemotherapeutic agents into the pericardium because of the risk of systemic toxicity. We believe it is probably not necessary to do so since none of our patients had a clinically significant recurrence of effusion even without the use of these agents. Possibly the thorough evacuation of all fluid allows coaptation of the visceral and parietal layers and the early formation of enough adhesions to prevent reaccumulation. It will be necessary to observe more patients over a longer period of follow-up to be certain of this. We believe the safety and immediate and long-lasting efficacy of subxiphoid pericardial window commend the procedure as the treatment of choice for all malignant pericardial effusions.

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Discussion

DR. JOSEPH C. KISER (Minneapolis, MN): I thank Dr. Hankins for reminding us of the efficacy of inferior pericardiotomy for drainage of pericardial effusion. The inferior approach was described by Larrey in 1829 but has not been widely practiced. Since pericardial lymphatics are singularly lacking, there being none in the parietal and few in the visceral location, the pericardial space is quite susceptible to loculation of fluid. This can result in hemodynamic derangement or inflammatory processes potentially leading to constrictive pericarditis.

Definition of significant pericardial effusion using echocardiography has obviated many of the previous cumbersome and uncertain methods. In my institution, patients with symptoms and findings suggestive of pericardial effusion are most often seen initially by the cardiologist. The technique of pericardiocentesis has become quite well standardized and is usually carried out as an initial procedure. The complications associated with pericardiocentesis, although unusual, include laceration of the heart or coronary artery, laceration of the internal mammary artery, penetration and possible contamination of the pleural cavity in cases of purulent pericarditis, laceration or puncture of the lung with resultant pneumothorax, aspiration of blood in the intracardiac chambers, and ventricular fibrillation. In some instances, pericardiocentesis is accompanied by the positioning of a thin-walled polyethylene catheter in the pericardial space. Even with serous effusion, recurrence of the effusion is not uncommon.

A cursory survey among my colleagues indicates that the anterior approach is most commonly used when a pericardial window is carried out. One of the worrisome complications from this procedure is chronic chondritis. Resection of the entire cartilage at the area of incision is usually done in an attempt to avoid this. The anterior approach may have advocates among those surgeons who are uncertain as to the form of effusion that is present and who think that a concomitant partial pericardiectomy through this same small incision when inflammatory forms of pericarditis are encountered may be desirable. In my experience, that might occur in as many as 40% of patients. I agree with Dr. Hankins that inferior pericardiotomy is a simple operation, which may be performed on very ill patients. It provides more thorough dependent drainage, allows for definitive diagnostic biopsy, and should be particularly valuable in those patients with malignant pericardial effusion.

I appreciate the opportunity of discussing this paper and congratulate Dr. Hankins and his associates for more carefully defining the technique of inferior pericardiotomy.

DR. SYED T. RAZA (Buffalo, NY): I congratulate Dr. Hankins for a very fine presentation, and will briefly review our experience at the Buffalo General Hospital with subxiphoid pericardial windows. Having been dissatisfied with pericardiocentesis, like many others, we started using subxiphoid pericardial windows in 1968. An initial report was published in The Annals several years ago (Ann Thorac Surg 19:47, 1975).

Our total experience to date comprises 90 patients of whom 49 had malignant effusions and 41 nonmalignant effusions. Causes of the malignant effusions include carcinoma of the lung (41%), carcinoma of the breast (35%), and lymphomas (16%). Carcinoma of the ovary, carcinoma with unknown primary, carcinoma of the cervix, and leukemia were a cause in a small number of patients.

Prior pericardiocentesis had been performed in 4 of the 49 patients, or 8%. Two of these patients required emergency pericardiocentesis to relieve symptoms of shock and hypotension before a subxiphoid window was made. The other 2 patients had pericardiocentesis on the insistence of our medical colleagues. Recurrent effusions developed in 3, or 6%, of the patients. In 1, the effusion occurred 2 days following the creation of a subxiphoid pericardial window when the tubes were clotted off and had to be reexplored; new chest tubes were inserted in the pericardial cavity. The other 2 patients were seen with recurring effusions at one week and 1 month following the initial procedure. A second pericardial window was successfully created in both patients.

We have had no complications or mortality related to this operation. However, the prognosis for these patients is generally poor because of carcinomatosis in most of them.

Based on this experience, I support Dr. Hankins's conclusions that the subxiphoid pericardial window is safe, easily performed, effective, and reliable. However, the prognosis depends on the extent of the primary disease.

DR. THOMAS EDWARD WILLIAMS (Columbus, OH): I, too, support the conclusions of Dr. Hankins and his colleagues and recommend inferior pericardiotomy in the treatment of malignant pericardial effusions. Since 1966, we at the Ohio State University have carried out inferior pericardiotomy for drainage of malignant effusions in approximately 26 patients. There have been three instances of recurrence requiring secondary drainage. One patient also required pericardiectomy. There were no deaths attributable to the procedure in the group of patients with malignant effusions.

Our cardiologists and our staff have gradually come to the conclusion that this really is our principal modality in the treatment of undiagnosed pericardial effusions of virtually any type, or of pericardial tamponade. In the last 14 or 15 years, we have carried out 180 or more inferior pericardiotomies with 1 death that we think should be attributed to the procedure. Complications related to the procedure that we have identified are pneumothorax and wound infections, both having an incidence of about 2%.

The operation is a relatively simple one. The patients have relatively large volumes of fluid. The pericardium rolls down in such a way that if the xiphoid process is removed, the operation is easy to perform.

This procedure is relatively definitive from both a therapeutic and a diagnostic standpoint. Specimens are obtained for bacteriological study and chemical determinations, and we simply place some heparin in a new sucker bottle and send all of that material for cytological study.

Dr. Hankins has made a very worthwhile presentation to this Society, and I compliment him and join the others in supporting the recommendations of him and his colleagues.

DR. HANKINS: I thank Drs. Kiser, Raza, and Williams for their remarks. I am glad that Dr. Kiser made the point about the danger of pericardiocentesis. We believe pericardiocentesis has no place in the diagnosis of malignant pericardial effusion, and very little place in the therapy. If the patient has symptoms and signs of a pericardial effusion and if the echocardiogram confirms or suggests this diagnosis, we go right ahead with the pericardial window. We believe the only indication for pericardiocentesis is in the occasional patient with rapidly increasing tamponade, and then it is done to relieve pressure and tide the patient over until the window procedure can be done.

I congratulate Dr. Raza on the large series of patients he presented. I am impressed that recurrent effusions developed in only 3 of his patients. I agree wholeheartedly that the prognosis for survival in patients with malignant pericardial effusion depends principally on the nature of the underlying primary malignancy.

Dr. Williams's series also was impressive. I congratulate him on his excellent results.

Notice from the American Board of Thoracic Surgery

The American Board of Thoracic Surgery now requires that candidates pass both the written and oral portions of the certifying examination.

In 1980 and thereafter, a written examination will be given *prior* to the oral examination. It will be necessary to pass the written examination before the oral examination can be taken. The closing date for registration for 1982 is August 1, 1981. The exact times and places of these examinations will be announced later.

A candidate applying for admission to the 1982 certifying examination must fulfill all the requirements for the Board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, 14640 E Seven Mile Road, Detroit, MI 48205.

Intramyocardial pH during Elective Arrest of the Heart: Relative Effects of Hypothermia versus Potassium Cardioplegia on Anaerobic Metabolism

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ABSTRACT **Using an intramyocardial pH needle probe (21 gauge) to monitor myocardial metabolism during ischemia, we determined the effect of potassium cardioplegia at both moderate and deep hypothermia. Five groups of 5 dogs each were placed on cardiopulmonary bypass and the pH probe was inserted approximately 10 mm into the left ventricular free wall. Cardiac ischemia was achieved by cross-clamping the ascending aorta at 37°C (Group 1), 27°C (Group 2), or 17°C (Group 3). In the remaining two groups, aortic cross-clamping was followed by the infusion of 600 to 800 ml of potassium cardioplegic solution adjusted to cardiac temperatures of 27°C (Group 4) or 17°C (Group 5). In each group, myocardial temperature was maintained constant, electrical and mechanical activity observed, and pH recorded until a plateau was reached or for 3 hours.**

Our results show a progressive and significant decrease in the metabolic rate with reduction in temperature over the 37° to 17°C range. By abolishing contractile activity, potassium cardioplegia markedly reduces the rate of hydrogen ion accumulation at 27°C, but at 17°C the additive effect of cardioplegia is much less pronounced. These observations support the principle of reducing contractile activity to a minimum during elective arrest of the heart but indicate that potassium cardioplegia does little to further reduce the rate of anaerobic metabolism, as shown by the measurement of intramyocardial pH, under conditions of deep hypothermia.

While elective arrest of the heart achieved by cross-clamping the ascending aorta plus aortic root perfusion with a cold cardioplegic solution has received widespread clinical acceptance as an adjunct to cardiac operation, the conditions for chemical cardioplegia are frequently not ideal. The cold arresting solution may be washed out by noncoronary collateral blood flow and myocardial temperature does not reach the temperature of the cardioplegic infusate, continually rises during the period of arrest, and can have a markedly nonhomogeneous distribution, particularly in the presence of coronary artery lesions [4, 13]. These factors, plus the differing extent of injury in the individual heart prior to cardiac operation, must introduce considerable variability in the tolerance to a given period of such elective arrest from one patient's heart to another.

On this basis, we reasoned that if information regarding the changing metabolic state of the myocardium could be monitored continuously under the conditions associated with elective arrest of the heart, it might be possible to manage myocardial protective techniques with more confidence in each individual case rather than drawing largely on past clinical experience and information from studies using experimental animals. Previously we explored the use of intramyocardial partial pressure of carbon dioxide as measured by mass spectrometry [17, 18] as a means of continuously monitoring the status of anaerobic metabolism in the ischemic myocardium. How-

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ever, due to technical limitations inherent to the mass spectrometric technique [23], we have shifted our emphasis to intramyocardial pH as measured potentiometrically by miniaturized electrodes. Having demonstrated that reliable and accurate monitoring of pH in cardiac tissue is possible and, moreover, that intramyocardial measurements of pH by implanted electrodes do reflect the state of intracellular metabolism during elective arrest of the heart [22], we have used our pH electrode system to examine the effects of potassium cardioplegia at progressively deeper levels of hypothermia (27°C and 17°C) on the changing state of anaerobic metabolism in the heart.

Material and Methods

Twenty-five adult mongrel dogs, weighing between 20 and 26 kg, were divided into five groups of 5 dogs each. In Groups 1, 2, and 3, simple ischemic arrest of the heart was performed at myocardial temperatures of 37°C, 27°C, and 17°C, respectively, whereas single-dose potassium cardioplegia in combination with global myocardial ischemia was used in Groups 4 and 5 at myocardial temperatures of 27°C and 17°C, respectively.

Each dog was placed on cardiopulmonary bypass as described previously [22] with the aortic root pressure maintained at 80 mm Hg by adjusting pump flow. When necessary, a cannula for delivering cardioplegic infusate was placed through the right subclavian artery into the aortic root. Specialized probes for continuously monitoring temperature and pH were then inserted into the left ventricular myocardium (Fig 1). The intramyocardial pH measurement system was described in detail previously together with the electrode calibration procedure and in vitro experiments to establish its accuracy in flowing blood [22].

In each dog, control conditions were first established with arterial blood gases maintained in a physiological range (pH, 7.35 to 7.45; partial pressure of carbon dioxide, 35 to 45 mm Hg; partial pressure of oxygen, over 100 mm Hg) and the myocardial temperature was adjusted to 37°C. The myocardial temperature was then either maintained at 37°C (Group 1) or reduced by adjusting the heat exchanger in the cardiopulmonary bypass circuit to 27°C (Groups 2 and 4) or to 17°C (Groups 3 and 5). The intramyocardial pH measurement system was precalibrated in vitro at the appropriate temperature level for the individual experiment before insertion of the pH and reference probes into the myocardium. No acid-base adjustments were made to those dogs which were cooled to either 27°C or 17°C; rather, the arterial blood pH and intramyocardial pH were allowed to move to new levels as intrinsically determined in each experimental preparation.

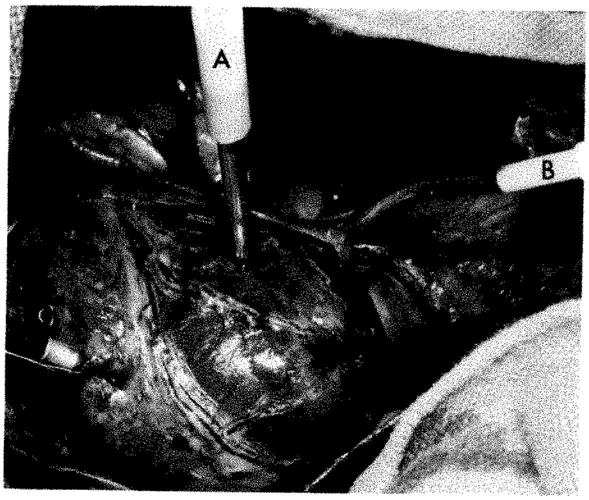


Fig 1. The pH probe (A), consisting of a 21 gauge hypodermic needle of 0.8 mm outside diameter and 13 mm length mounted on the end of a metal barrel and plastic connector hub through which the electrode is connected to an electrically shielded conductor cable, is inserted into the anterior free wall of the left ventricle to a depth of 10 ± 1 mm. The reference electrode (B), consisting of a silver–silver chloride internal electrode surrounded by a salt bridge solution of 150 mM per liter of sodium chloride saturated with silver chloride and housed in a flexible polyvinyl tube 2 mm in outside diameter with a microporous plug at its tip, is inserted superficially into the myocardium 1 to 2 cm from the needle pH probe. A needle-tip thermocouple probe (C) is placed in the interventricular septum.

Global myocardial ischemia was achieved at myocardial temperatures of 37°C, 27°C, and 17°C in Groups 1, 2, and 3, respectively, by clamping the proximal ascending aorta. In contrast, single-dose chemical cardioplegia was used at myocardial temperatures of 27°C and 17°C in Groups 4 and 5, respectively, with global myocardial ischemia achieved by placing the cross-clamp across the aortic arch immediately beyond the cardioplegia infusion cannula

Table 1. Composition of Cardioplegic Solution[a]

Cations		Anions	
K^+	40 mEq/L	Cl^-	67 mEq/L
Na^+	27 mEq/L		
Mg^{++}	6 mEq/L	$SO_4^=$	6 mEq/L

[a] Vehicle, 5% dextrose in water; osmolarity, 380 mOsm; buffer, tromethamine to desired pH (7.4 to 7.8).

with the right carotid artery occluded to avoid loss of the cardioplegic infusate. Infusion of 600 to 800 ml of cardioplegic solution into the aortic root, using a pump at a controlled rate of 400 ml per minute, was begun within three seconds of cross-clamping. The constituents of the cardioplegic infusate are presented in Table 1. The cardioplegic solution was prepared fresh during each experiment, and the amount of tromethamine buffer was varied so that the pH of the solution was approximately that of the intramyocardial pH indicated by our electrode system. The cardioplegic infusate was maintained at the same temperature as the myocardium, 27°C for Group 4 and 17°C for Group 5, by immersion of the infusion bag in a temperature-controlled water bath.

Observations of both mechanical activity of the heart by direct visual inspection and electrical activity of the heart from the electrocardiogram were performed following cross-clamping of the aorta. The time elapsed to ventricular standstill was noted when chemical cardioplegia was used, and a record was kept of the electrical and mechanical activity at 1-minute intervals for the first 15 minutes and at 5-minute intervals thereafter during the period of elective global myocardial ischemia, which was maintained until the intramyocardial pH had reached a stable plateau value or until 180 minutes had passed, whichever occurred first. This required a 120-minute ischemic period at 37°C (Group 1) and 180 minutes of ischemia at 27°C (Groups 2 and 4) and at 17°C (Groups 3 and 5). Special care was taken to maintain myocardial temperature constant to within ±1°C during the entire ischemic period in all groups by a combination of methods: adjusting the heat exchanger of the cardiopulmonary bypass circuit, covering the thoracotomy site to reduce convective heat transfer, and applying radiant heat from an infrared light source or ice packs for cooling, as appropriate, to the chest wall. During the ischemic period, the pump flow in the cardiopulmonary bypass circuit was reduced to yield an aortic pressure of 50 mm Hg in an attempt to limit noncoronary collateral blood flow to the myocardium.

At the termination of the ischemic period, cardiopulmonary bypass was discontinued, reperfusion of the heart not being performed. The needle pH probe, reference electrode, and temperature probe were removed from the heart, their sites were checked by dissecting through their tracts in the myocardium, and the pH measurement system recalibrated.

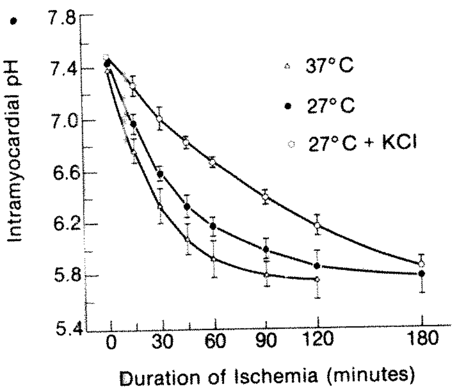
The intramyocardial pH data from the five experimental groups were compared by the application of Student's *t* test for unpaired data with two-tailed confidence limits set at 95% for statistical significance.

Results

Intramyocardial pH

A comparison of the profiles of intramyocardial pH plotted against the duration of global myocardial ischemia for 37°C (Group 1), 27°C (Group 2), and 27°C + potassium cardioplegia (Group 4) is presented in Figure 2. The results clearly indicate substantial additive benefits of combining moderate hypothermia (27°C) with potassium cardioplegia at that temperature on lowering the rate of accumulation of hydrogen

Fig 2. The profiles of intramyocardial pH (mean ± standard deviation) plotted against the duration of global myocardial ischemia are compared for 37°C (Group 1), 27°C (Group 2), and 27°C + KCl cardioplegia (Group 4).



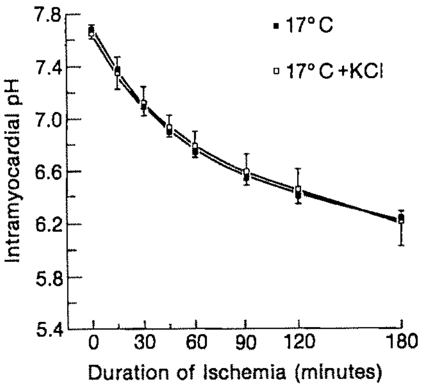


Fig 3. The profiles of intramyocardial pH (mean ± standard deviation) plotted against the duration of global myocardial ischemia are compared for 17°C (Group 3) and 17°C + KCl cardioplegia (Group 5).

ions in the myocardium during the ischemic period. The differences between 37°C (Group 1) and 27°C (Group 2), which demonstrate the effect of moderate hypothermia alone, were significant at 99% confidence limits at all times between 15 and 60 minutes. However, the differences between 27°C (Group 2) and 27°C + potassium cardioplegia (Group 4), which demonstrate the additive effect of potassium cardioplegia at moderate hypothermia, were even more striking, with statistical significance demonstrated at 99.9% confidence limits at all times between 15 and 120 minutes.

In Figure 3, the intramyocardial pH profiles for 17°C (Group 3) and 17°C + potassium cardioplegia (Group 5) are plotted against the duration of global myocardial ischemia. The contrast with the results presented in Figure 2 is striking. Potassium cardioplegia does not appear to have the additive effect at 17°C on lowering the rate of hydrogen ion accumulation that is clearly demonstrated at 27°C. Statistical comparison of the pH data for 17°C (Group 3) versus 17°C + potassium cardioplegia (Group 5) revealed no significant difference in the absolute pH measured at any time from 0 to 180 minutes. The intramyocardial pH levels at the onset of ischemia were 7.68 ± 0.05 units (mean ± standard deviation) for 17°C (Group 3) and 7.65 ± 0.07 units for 17°C + potassium cardioplegia (Group 5), both of which were significantly ($p < 0.005$) different from the initial pH levels of 7.44 ± 0.05 at 27°C and 7.41 ± 0.06 at 37°C due to the adjustments in the pH of circulating blood and, therefore, the myocardial interstitium during the cooling process. Because of this difference in pH levels at the onset of global myocardial ischemia, it is potentially misleading to compare the plots of absolute pH at 37°C (Group 1), 27°C (Group 2), and 27°C + potassium cardioplegia (Group 4) in Figure 2 with plots of absolute pH at 17°C (Group 3) and 17°C + potassium cardioplegia (Group 5) in Figure 3. For this reason, the data are presented in two separate graphs.

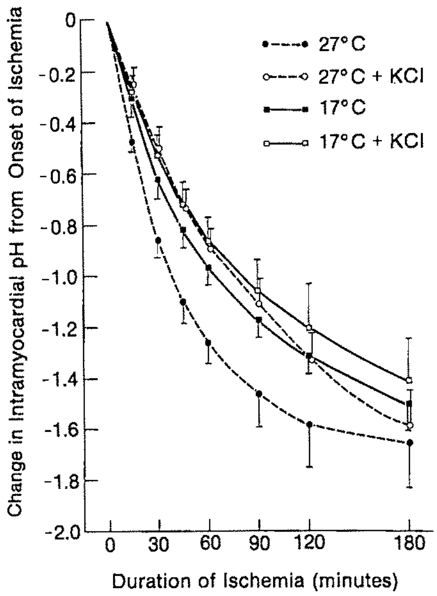


Fig 4. The change in intramyocardial pH (mean ± standard deviation) from the onset of ischemia is plotted against the duration of global myocardial ischemia for 27°C (Group 2), 27°C + KCl cardioplegia (Group 4), 17°C (Group 3), and 17°C + KCl cardioplegia (Group 5).

A more sensitive technique for comparing the effects of potassium cardioplegia on the profiles of intramyocardial pH under the differing degrees of hypothermia examined in this study is to plot the change in intramyocardial pH from the onset of global myocardial ischemia against the duration of ischemia. This approach (Figure 4) overcomes the problem of differences in the absolute value of intramyocardial pH at the onset of ischemia. Table 2 presents data relating to the change in intramyocardial pH for all five groups of this study with statistical comparisons.

The increasing benefit of progressively deeper levels of hypothermia on reducing the

Table 2. Change in Intramyocardial pH from the Onset of Ischemia[a]

Group and Comparison[b]	Duration of Global Myocardial Ischemia (min)						
	15	30	45	60	90	120	180
1. 37°C	−0.63 ± 0.08	−1.07 ± 0.14	1.33 ± 0.13	1.48 ± 0.16	−1.55 ± 0.12	−1.62 ± 0.16	−1.62 ± 0.16
versus	$p < 0.005$	$p < 0.01$	$p < 0.01$	$p < 0.025$	NS, $p > 0.10$	NS, $p > 0.5$	NS, $p > 0.5$
2. 27°C[c]	−0.46 ± 0.03	−0.86 ± 0.06	−1.10 ± 0.09	−1.26 ± 0.09	1.47 ± 0.13	−1.59 ± 0.16	−1.66 ± 0.19
versus	$p < 0.005$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.005$	$p < 0.01$	NS, $p > 0.1$
3. 17°C	−0.30 ± 0.08	−0.62 ± 0.08	−0.82 ± 0.06	−0.97 ± 0.06	−1.17 ± 0.7	−1.31 ± 0.07	−1.49 ± 0.09
versus	NS, $p > 0.5$	NS, $p > 0.1$	$0.1 > p > 0.05$	$0.1 > p > 0.05$	NS, $p > 0.1$	NS, $p > 0.1$	NS, $p > 0.2$
5. 17°C + KCl	−0.29 ± 0.06	−0.53 ± 0.09	−0.72 ± 0.09	−0.86 ± 0.10	−1.06 ± 0.13	−1.19 ± 0.17	−1.39 ± 0.18
versus	NS, $p > 0.4$	NS, $p > 0.5$	NS, $p > 0.5$	NS, $p > 0.5$	NS, $p > 0.4$	NS, $p > 0.1$	$0.1 > p > 0.05$
4. 27°C + KCl[c]	−0.25 ± 0.08	−0.49 ± 0.10	−0.73 ± 0.10	−0.88 ± 0.08	−1.11 ± 0.09	−1.33 ± 0.09	−1.59 ± 0.14

[a] All values are mean ± standard deviation.

[b] Student's t test on unpaired data.

[c] A comparison of 27°C + potassium cardioplegia (Group 4) with 27°C (Group 2) shows significant differences ($p < 0.01$) at all times between 15 and 120 minutes.

NS = not significant.

Table 3. Myocardial Mechanical and Electrical Activity

Experimental Group	Range in Duration of Activity (min)	
	Mechanical	Electrical
1. 37°C	10 to 25	30 to 40
2. 27°C	8 to 20	15 to 35
3. 17°C	20 to 40	30 to 60
4. 27°C + KCl	< 0.5	< 0.5
5. 17°C + KCl	< 0.5	< 0.5

rate of accumulation of hydrogen ions in the myocardium is apparent at both 27°C (Group 2) compared with 37°C (Group 1) and 17°C (Group 3) compared with 27°C (Group 2). The marked effect of potassium cardioplegia at moderate hypothermia (27°C) is also evident but its influence at deep hypothermia (17°C) is small. The differences between 17°C (Group 3) and 17°C + potassium cardioplegia (Group 5) after 45 to 60 minutes of ischemia closely approach, but do not satisfy, the confidence limits set conventionally at 95% for statistical significance. With only 5 dogs in each group, the sample sizes are small for statistical purposes and, therefore, a statistically significant additive effect of potassium cardioplegia on the profile of intramyocardial pH could likely be demonstrated by substantially increasing the numbers of dogs studied at 17°C. However, even assuming this to be the case, the present data indicate that any such additive effect on slowing the accumulation of hydrogen ions in the myocardium is much smaller than the effect observed at 27°C.

Myocardial Mechanical and Electrical Activity

A comparison of the total duration of myocardial mechanical and electrical activity during ischemia in Groups 1 to 5 is presented in Table 3. In all the groups that did not have potassium cardioplegia, the left ventricle continued to beat regularly for at least 2 minutes after the onset of global myocardial ischemia. Mechanical activity in the form of either ventricular fibrillation or regular contractions continued for several more minutes and was highly variable in both duration, as indicated in Table 3, and in apparent intensity, as assessed qualitatively by observing the waves of contraction on the anterior surface of the left ventricle, with the apparent strength of organized contractions or fibrillation gradually declining over several minutes in each case. On the other hand, complete electromechanical arrest was always achieved within 0.5 minute of the onset of infusion of the potassium cardioplegic solution and, once electromechanical standstill was achieved, there was no return of electrical or mechanical activity for the remainder of the duration of global myocardial ischemia.

Comment

Progressively deeper levels of hypothermia are generally accepted to afford increasing myocardial protection during elective arrest of the heart in cardiac operations, but the additive benefit of potassium cardioplegia under conditions of deep hypothermia is still controversial. Our findings do support the principle of reducing contractile activity to a minimum in order to reduce the rate of anaerobic metabolism during elective arrest of the heart. However, while we have shown that potassium cardioplegia produces a substantial reduction in metabolic rate under moderate hypothermia (27°C), we found that this additive benefit is much smaller under conditions of deep hypothermia (17°C). Evidence has accumulated from studies using different experimental models to show that additive protection, as assessed on the basis of postarrest hemodynamic function and morphology, is conferred by chemical cardioplegia at temperature levels in the range of 24° to 28°C [1, 2, 16]. At lower myocardial temperatures, in the range of 12° to 15°C, Engelman and his colleagues asserted that there is additive protection conferred by multidose potassium cardioplegia over simple ischemia on the basis of measurements of ventricular function [6, 8] and myocardial levels of adenosine triphosphate and creatine phosphate [9]. The extent to which the added benefit of multidose potassium cardioplegia at profound hypothermia depends on washout of accumulated metabolites from the myocardium compared with the arresting effect of the cardioplegic solution itself has not, to our knowledge, been reported. However, with single-dose cardioplegia, as performed in the present study, Engelman and associates [7] could not demonstrate any significant advantage over simple ischemic arrest of 60 minutes duration when the myocardial temperature was maintained between 12° to 15°C in both groups. More recently, Kay and colleagues [16] stated, on the basis of both hemodynamic and morphological criteria, that additive protection is conferred by single-dose potassium cardioplegia over simple ischemia of 90 minutes duration at 11°C. Our intramyocardial pH data are consistent with the presence of some additive protection by potassium cardioplegia over hypothermia at and below 17°C, but they do suggest that at these low temperatures a point of diminishing returns has been reached. This impression is compatible with recent clinical experience in which lowering the potassium ion concentration of a single-dose cold cardioplegic infusate to normal levels made no measurable difference to the degree of myocardial protection [5, 21].

It is also conceivable that, at lower temperatures, there is a dissociation between the extent of protection afforded by potassium cardioplegia and the much lesser apparent advantage inferred from measurements of the profile of intramyocardial pH under these conditions. However, Bretschneider and associates [3] demonstrated a close correlation between intramyocardial pH and high-energy phosphate concentrations under ischemic conditions over a wide range of temperatures down to 15°C, both with and without chemical cardioplegia. Furthermore, their data suggest that the lowest intramyocardial pH obtained during a single period of global myocardial ischemia and compatible with recovery of hemodynamic function is approximately 6.3 pH units and is independent of the presence or absence of chemical cardioplegia. In 1979, Schaper and Knoll [20] reported that in human myocardial biopsies exposed to in vitro conditions of complete ischemia at 15°C, there is considerable variability in the rate of decline of pH but a good correlation between the interstitial pH and ultrastructural criteria for myocardial injury, a pH level below 6.3 indicating irreversible damage. They concluded that interstitial pH is an exact indicator of the cellular tolerance limit to ischemia.

Further experimental studies will be needed to establish the relationship of intramyocardial pH levels during elective arrest of the heart, under conditions of temperature and chemical cardioplegia similar to those that pertain clinically, to cellular viability following reperfusion. The relationship between intramyocardial pH and postarrest left ventricular hemodynamic function also clearly deserves further study. However, one must be aware that the relationship between moderate degrees of depression in hemodynamic function in the early hours of the postarrest period and the extent of irreversible cell injury in the myocardium has not yet been well defined. Furthermore, the interpretation of left ventricular function data in available experimental models is complicated on one hand by an isovolumic constraint to ventricular contractions when a left ventricular intracavitary balloon is inserted [2, 6, 8] and, on the other hand, by lack of information concerning changes in compliance of the left ventricle when Sarnoff [19] function curves obtained by volume loading are used [1, 16].

We used only one cardioplegic formulation (see Table 1) in this study, and it is possible that a different arresting solution might be able to provide a greater additive benefit in slowing the rate of anaerobic metabolism at or even below 17°C. The composition of our cardioplegic solution certainly does not appear ideal in that the ratio of potassium ion concentration to sodium ion concentration is high and could be detrimental in raising the rate of calcium influx into the cell, as suggested by Gharagozloo and associates [11]. On the other hand, the solution is calcium free with some potential for damage on this basis alone [15], although the tendency for a calcium-deficient cardioplegic solution to be replaced with normocalcemic blood on the basis of even a small amount of noncoronary collateral blood flow probably alleviates this problem both in our experimental model and clinically. Finally, the glucose concentration of our cardioplegic formulation is high, and this too, according to Hearse and colleagues [12], may be a problem. Nevertheless, we consider that the most likely explanation for our observations is that, as the temperature is lowered to 17°C, the absolute difference in rate of anaerobic metabolism in the heart in complete electromechanical standstill, as contrasted with the beating or fibrillating state, is small in comparison with the higher temperatures. According to this proposition, complete electromechanical arrest is, in theory, desirable at any temperature level but its practical importance under conditions of deep hypothermia is minimal. Examined from a different perspective, our pH data (see Fig 4; Table 2) also indicate that potassium cardioplegia at 27°C is about as effective as further cooling to 17°C in reducing the rate of hydrogen ion accumulation. Thus, the use of cold chemical cardioplegia may provide an added safety factor for areas of the heart in which the temperature tends to rise, provided electromechanical standstill can be maintained.

An alternative approach to the measurement of intramyocardial pH not involving the insertion of any probes in the myocardium is the technique of phosphorus nuclear magnetic resonance [14]. This method offers major advantages in that the measurements are both noninvasive and intracellular although, at present, its use is limited to isolated heart preparations from small species (rat and rabbit) suspended in the large electromagnet required to produce the magnetic resonance [14]. Flaherty and colleagues [10] studied the effects of potassium cardioplegia at 27°C on anaerobic metabolism in the rabbit heart using the phosphorus nuclear magnetic resonance technique, and their findings are similar to ours in demonstrating an additive benefit of potassium cardioplegia at moderate hypothermia.

Intramyocardial pH measurements are subject to an inherent limitation in that they fully reflect the metabolic state of the myocardium only under the condition of total cessation of blood flow. With perfusion, hydrogen ions are carried away in the venous outflow. Thus, with multidose chemical cardioplegia, one would expect the intramyocardial pH and partial pressure of carbon dioxide to decline during each ischemia period and then return toward normal with each reinfusion of cardioplegic solution. The interpretation of such measurements would clearly be more complex than for single-dose cardioplegia as addressed in the present study. However, the monitoring of intramyocardial pH could nonetheless be quite valuable under these conditions. One could envision placing a pH probe in a region of myocardium (e.g., the subendocardium of a hypertrophic left ventricle or an area supplied by a severely stenosed coronary artery) particularly susceptible to injury during the procedure of elective arrest of the heart. The pH level could be used as a guide for the timing of reinfusion of the cardioplegic solution, and the resulting return of intramyocardial pH toward baseline conditions would confirm the effectiveness of metabolite washout from the coronary microcirculation. It might also be possible to establish empirically a practical safe lower limit on intramyocardial pH under these conditions. On this basis, the intramyocardial pH measurement system would either provide the reassurance that the metabolic limits of cellular viability had not been exceeded or indicate an impending failure in myocardial protection so that corrective action could be taken. There is a growing recognition of the importance of attention to detail in the technique of chemical cardioplegia, as distinct from the basic principles which are now firmly established. The on-line monitoring of intramyocardial pH could provide an important check on technique.

In this study, we have demonstrated the use of intramyocardial pH measurements to monitor anaerobic metabolism in the context of elective arrest of the heart under widely differing conditions. We recognize that instrumentation for this approach to continuously monitor myocardial metabolism will require substantial improvements and that questions concerning the relationship of intramyocardial pH levels to postarrest cellular viability and hemodynamic function must be answered before clinical application becomes practical. However, we do believe that a system for continuously monitoring tissue pH in the individual patient's heart can be of great use in the context of cardiac operation and that, with improved technology, such measurements will become a clinical reality.

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Discussion

DR. TIMOTHY J. GARDNER (Baltimore, MD): This presentation by Dr. Wilson reflects very well the careful, thorough, and well-reasoned research efforts of Drs. Wilson and MacGregor and their colleagues. It raises at least two important issues, one dealing with the method of monitoring myocardial metabolic activity during ischemia, namely, myocardial pH monitoring, and the other potentially more significant issue deals with one's approach to the use of cold chemical cardioplegia.

Regarding extracellular pH monitoring as employed by Dr. Wilson in these experiments, I agree that it is a valid method of monitoring myocardial metabolic activity, primarily anaerobic, during conditions of global cardiac ischemia. Although pH monitoring is less costly to use than the mass spectrometer or a nuclear magnetic resonance apparatus, it is not as useful as the latter for laboratory studies and probably not usable in its present state for the types of clinical studies in which myocardial gas tension monitoring with mass spectrometry has been used.

But clearly more important an issue than that of research methodology is Dr. Wilson's implied or tentative conclusion that at a myocardial temperature of 17°C, whether one uses cooling alone or infusion of chemical cardioplegia may be of no great consequence. Even such a tentative conclusion, however, is unwarranted on the basis of this study, which measures only one element of myocardial protection—metabolic activity during the period of global ischemia. The most valid criterion of the degree of protection during induced ischemia is the extent of preservation of ventricular function. In this study, no functional data are provided, and I find it difficult, therefore, to interpret the study.

I have two questions for Dr. Wilson. Why do you think that hearts that continued to beat at 17°C have the same level of metabolic activity as the potassium-treated hearts, which were rendered asystolic? Second, why did you use a hyponatremic cardioplegic solution, which may in itself be injurious to the myocardium?

DR. THOMAS Z. LAJOS (Buffalo, NY): I congratulate the authors for another excellent paper on pH and metabolic derangements in the arrested heart. My associates and I were interested in this problem in a slightly different fashion, and our present cardioplegic technique in the operating room allows us to analyze the coronary sinus flow selectively. As a result, we have analyzed the coronary sinus pH changes and the appearance of the CPK-MB isoenzyme.

We found that there is a definite correlation between the decrease of pH and the appearance of the CPK-MB isoenzyme at the level of 7.15. However, we could not correlate or assess the degree of damage. Dr. Wilson, what do you think about this correlation? While pH changes are good indications that there is some damage or metabolic derangement in the heart muscle, the quantification of that damage by this method is not accurate and may cause difficulties.

DR. WILSON: I thank Dr. Gardner and Dr. Lajos for their comments. In regard to Dr. Gardner's question concerning why the group of hearts arrested at 17°C with chemical cardioplegia should provide a pH profile that was the same as that of hearts at the same temperature which continue to have electromechanical activity, our results do suggest that there is a small difference favoring cardioplegia between these groups. This small difference fell just short of satisfying the 95% confidence limits in our statistical analysis. Our interpretation of these findings is that as the temperature is lowered to 17°C, the absolute difference in the rate of myocardial anaerobic metabolism in complete electromechanical standstill, as contrasted with the beating or fibrillating state, becomes small in comparison with the differences observed at higher temperatures. On this basis, complete electromechanical arrest is theoretically desirable at any temperature level but its practical importance in deep hypothermia is minimal.

In regard to our cardioplegic solution being hyponatremic and, therefore, not ideal, this point is certainly well taken. Our rationale for using this solution was that it is similar to what is used clinically at our center at present. It may, indeed, be possible with an optimized cardioplegic solution to obtain larger differences in protection over simple ischemia at lower temperatures, and this is an area we intend to explore in more detail.

Dr. Gardner's statement that pH monitoring is probably not usable for clinical studies in its present state is valid, but with improved technology it offers the potential of a system for clinical use clearly superior to mass spectrometry in size of probe, localization of measurement, dynamic response, compensation for effects of temperature variation, and cost. It is because of this potential that we have shifted our emphasis away from mass spectrometry with which we have had considerable experience. In regard to phosphorus nuclear magnetic resonance, there is no doubt that this is an elegant method for metabolic studies in the laboratory setting. However, the equipment is of enormous expense, its use has been limited to small isolated heart preparations (rats and rabbits) which do not meet all experimental needs, and its pH values are calculated, involving inherent assumptions, not directly measured. Every measurement system has its limitations. Nevertheless, we are impressed by the technique and will watch with interest for further developments.

Dr. Gardner has expressed reservations about drawing firm conclusions from our study in regard to the additive benefit of potassium cardioplegia in combination with deep hypothermia on the basis that only a single variable, pH, was measured. I would agree that before making a dogmatic statement, which I have taken care to avoid, one has to look at the correlation between intramyocardial pH and postarrest hemodynamic function, as he mentioned. I will add that the interpretation of hemodynamic function data in the early hours of the postarrest period is also not without its problems and suggest that postarrest morphological assessment of irreversible myocardial cell damage may be of more fundamental value. In fact, we are proceeding with such studies relating to both structure and function in the postarrest period.

Regarding the experience which Dr. Lajos has related, it is difficult for me to provide a specific response without being more familiar with the details of his measurements. Of course one must be cautious in expecting too much of the measurement of a single factor in either the experimental or clinical setting, but I believe that the capability for continuous monitoring of the metabolic status in the individual patient's heart in a cardiac operation can be of great use, and, while this goal is a difficult one, it is worth pursuing.

Acquired Left Ventricular–Right Atrial Fistula Following Aortic Valve Replacement

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and Stewart M. Scott, M.D.

ABSTRACT **Intracardiac communications produced as a complication of valve replacement can result in left-to-right shunts and a poor surgical result. The successful surgical closure of a left ventricular–right atrial fistula following aortic valve replacement is discussed. The intricate relationships of the membranous interventricular septum, the aortic, mitral, and tricuspid valves, and the aortic root predispose to the creation of abnormal intracardiac shunts when aggressive debridement of extensive valvular calcification is performed at the time of valve excision and replacement.**

Prosthetic valve replacement has markedly improved both the survival and quality of life for the majority of patients with clinically significant acquired valvular disease. Only a small percentage of patients manifest no clinical improvement following valve operation. Perivalvular leaks, prosthetic valve dysfunction, uncorrected associated valvular lesions, and irreversible myocardial disease have been found most frequently at repeat cardiac catheterization as the explanation for these poor surgical results [8].

Iatrogenically induced intracardiac communications, inadvertently produced during valve replacement and resulting in large left-to-right shunts, are another mechanism of failure of hemodynamic improvement following valve operation (Table) [2–10]. The present report describes the successful surgical closure of a left ventricular–right atrial shunt in a patient seen with recurrent congestive heart failure two years after aortic valve replacement.

A 67-year-old man was admitted to the Asheville Veterans Administration Hospital in February, 1975, with severe dyspnea on exertion and angina pectoris. Pertinent physical findings included a blood pressure of 130/60 mm Hg, normal pulses and rhythm, cardiomegaly, a grade 4/6 harsh ejection murmur radiating into the carotid area, and a 2/6 blowing diastolic murmur. Chest roentgenogram and electrocardiogram (ECG) showed left ventricular hypertrophy. Right heart and transseptal left heart catheterization revealed a peak systolic gradient of 70 mm Hg across a heavily calcified aortic valve, 2+ aortic valve incompetence, and elevated pulmonary artery pressures (40/20 mm Hg). There were no other valvular lesions. Coronary arteriograms and oxygen saturations were normal. In April, 1975, a heavily calcified tricuspid aortic valve was replaced with a No. 9 Starr-Edwards model 2400.

The patient had complete relief of symptoms until July, 1977, when he began to experience dyspnea on exertion, orthopnea, and paroxysmal noctural dyspnea. He also had hemolytic anemia. Despite vigorous medical therapy, the patient's symptoms of congestive heart failure became worse, and he was readmitted to the hospital in September, 1977. He had a blood pressure of 110/50 mm Hg, an irregularly irregular pulse, prominent *v* waves, biventricular enlargement, 4/6 systolic and diastolic murmurs at the left sternal border, hepatomegaly, and pretibial edema. Chest roentgenogram showed cardiomegaly and pulmonary vascular congestion and the ECG, atrial fibrillation and left ventricular hypertrophy with strain. Cardiac catheterization demonstrated mild perivalvular insufficiency, a 10 mm Hg transvalvular gradient, 2+ mitral and tricuspid regurgitation, elevated pulmonary artery pressures

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Previously Reported Intracardiac Shunts Acquired Following Prosthetic Valve Replacement

Authors	No. of Patients	Site of Fistula	Valve Replaced	Comment	Treatment	Result
Galbraith et al [2]	1	LV–RA	Aortic	Acute congestive failure in perioperative period	Closure of fistula through right atriotomy	Good
	2	LV–RA	Aortic	Congestive failure 2 mo postop	Closure of fistula through right atriotomy	Good
Roberts et al [9]	1	VSD	Aortic	Found at postmortem examination; thought to be hemodynamically insignificant	None	. . .
Timmis et al [10]	1	Atrial septum	Aortic replacement, mitral commissurotomy	Congestive failure 2 yr postop; atrial septum incised at original operation	None	Died after repeat catheterization
	2	Atrial septum	Aortic and mitral	Congestive failure 18 mo postop	Septal defect closed primarily	Died
Marsten and Hildner [5]	1	LV–RA	Mitral	Persistent congestive failure post-op	Closure of fistula through right atriotomy	Good
	2	LV–RA	Mitral	Defect noted during mitral valve replacement	Closure of fistula through atriotomy	Died
Jupa and Carleton [4]	1	Aorta–RV	Aortic	New murmur noted 9 d postop	None	Symptomatic
Miller et al [6]	1	LV–coronary sinus	Mitral	Persistent heart failure after repeat mitral valve replacement	Closure of fistula through right atriotomy	Good
Morritt et al [7]	1	LV–coronary sinus	Mitral	Persistent heart failure after repeat mitral valve replacement	Closure of fistula through right atriotomy	Good
Jackson et al [3]	1	Aorta–RA and RV	Aortic	Recurrent congestive failure 9 mo postop	Closure of fistulas through aorta and right ventricle	Died
	2	LV–RA and RV	Aortic	Recurrent congestive failure 6 mo postop	Patch closure of fistula through right ventriculotomy	Died
Silverman et al [this report]	1	LV–RA	Aortic	Congestive failure 2 yr postop	Closure of fistula through right atriotomy	Good

LV = left ventricle; RA = right atrium; VSD = ventricular septal defect; RV = right ventricle.

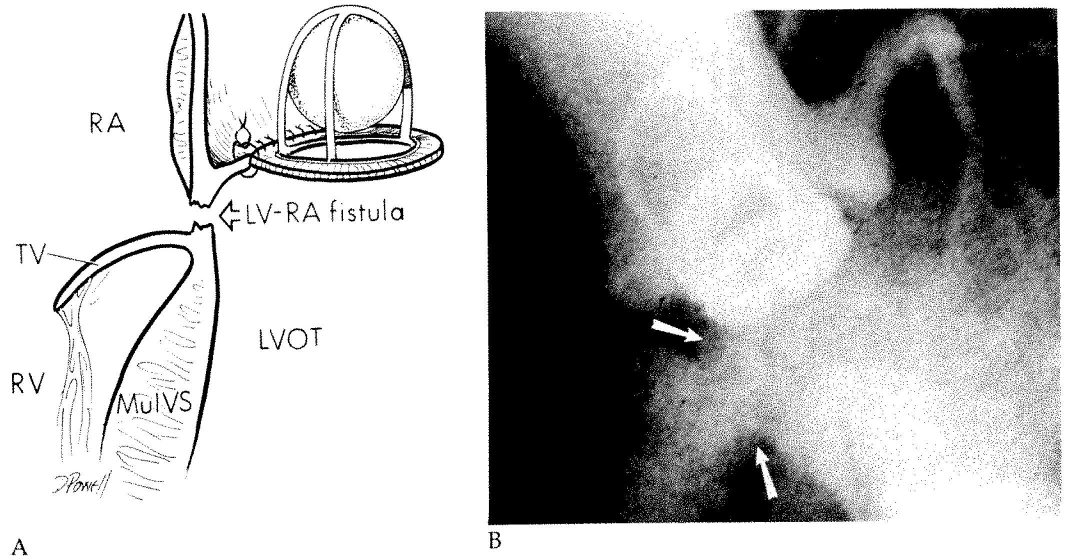

Fig 1. (A) Site of the left ventricular–right atrial (LV–RA) *fistula located in the membranous ventricular septum below the prosthetic aortic valve. There is no paravalvular leak. (B) Cineangiogram of left ventricular injection showing the dye crossing the fistula* (arrow) *into the right atrium.* (RA = *right atrium;* TV = *tricuspid valve;* RV = *right ventricle;* LVOT = *left ventricular outflow tract;* MulVS = *muscular ventricular septum.)*

(75/25 mm Hg), a ventricular–right atrial shunt with a pulmonary/systemic flow ratio of 2.5 : 1, and an appreciable oxygen step-up at the atrial level (Fig 1).

Reoperation was performed in October, 1977. There was a prominent thrill over the right atrium and the left ventricular outflow tract. Digital exploration through the right atrial appendage revealed a large jet of blood across the atrial septum just above the tricuspid annulus. Inspection of the aortic prosthesis showed no periprosthetic leak or cloth wear. Through a right atriotomy, a 5 mm defect lying just cephalad to the septal leaflet of the tricuspid valve was revealed. A probe passed through the defect could be introduced into the left ventricular outflow tract beneath the aortic annulus in the noncoronary region. The defect was closed with interrupted pledgeted sutures. The patient did well, although the postoperative course was protracted by respiratory insufficiency. When examined at an eighteen-month follow-up visit, he had a 1+ diastolic murmur but no clinical evidence of congestive heart failure.

Comment

Although congenital left ventricular–right atrial communication is a well-documented entity, it is clear that the patient described had an acquired fistula. It is unlikely that this communication was a complication of the initial transseptal left heart catheterization. Walmsley and Watson [11] carefully described the anatomy of the medial wall of the right atrium. In transverse sections of the heart above and below the level of the aortic valve, the medial wall of the right atrium is related anteriorly to the membranous interventricular septum and ascending aorta and only posteriorly, through the interatrial septum, to the left atrium (Fig 2). Inadvertent puncture of the medial atrial wall by the transseptal catheter just superior to the insertion of the septal leaflet of the tricuspid valve could cause a left ventricular–right atrial communication. However, because no shunt was noted by oximetry later in the first catheterization in the patient reported here, it is more likely that the fistula was due to operative trauma at the initial aortic valve replacement.

Edwards and Burchell [1] outlined the intricate relationships between the membranous portion of the ventricular septum, the aortic, mitral, and tricuspid valves, the right atrium, and both ventricles. The thin membranous septum lies immediately beneath the anterior half of the noncoronary aortic cusp. Anteriorly it merges with the muscular ventricular septum, while posteriorly it merges with the an-

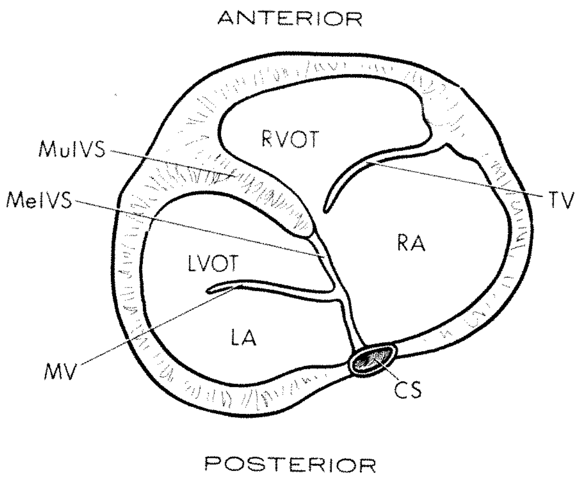

Fig 2. Transverse section of a heart at a level below the aortic annulus. (RVOT = *right ventricular outflow tract;* MulVS = *muscular ventricular septum;* TV = *tricuspid valve;* MelVS = *membranous ventricular septum;* RA = *right atrium;* LVOT = *left ventricular outflow tract;* MV = *mitral valve;* LA = *left atrium;* CS = *coronary sinus.)*

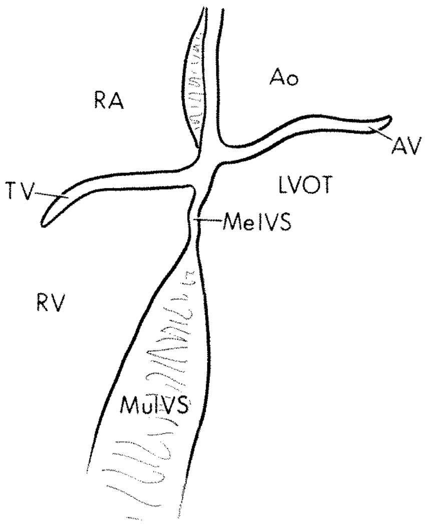

Fig 3. Coronal section of a heart illustrating the tricuspid valve (TV) *separating the membranous ventricular septum* (MelVS) *into its interventricular and ventriculoatrial portions.* (RA = *right atrium;* Ao = *aorta;* AV = *aortic valve;* LVOT = *left ventricular outflow tract;* RV = *right ventricle;* MulVS = *muscular ventricular septum.)*

nulus fibrosis of the atrioventricular valves. The septal leaflet of the tricuspid valve attaches on the membranous septum, dividing it into an anterior portion that separates both ventricles and a posterior partition between the left ventricle and right atrium (Fig 3).

During aortic valve replacement, these anatomical relationships must be appreciated to avoid operative injury to important structures. When debriding calcium from the annulus to provide a compliant bed for valve seating, aggressive dissection under the right coronary cusp can cause injury to the conduction system. Similarly, aggressive debridement below the noncoronary cusp can cause injury to the membranous septum or the mitral valve apparatus. This excessive debridement or trauma from retraction most likely produced the fistula described in our patient. A similar mechanism was suggested by Galbraith and co-workers [2] in their 2 patients with acquired left ventricular–right atrial shunts following aortic valve operation.

A left ventricular–right atrial fistula has been reported also following mitral valve replacement [5]. Again, aggressive debridement of areas of calcification was proposed as the cause. During excision of the aortic leaflet of the mitral valve, removal of calcium in the posteromedial commissure may result in laceration of the membranous septum. Marsten and Hildner [5] suggested accepting an asymmetrical seat for the prosthetic sewing ring rather than risking injury to the atrioventricular septum.

Although infrequent, other iatrogenic intracardiac shunts have been reported following valve replacement. Timmis and associates [10] reported 2 patients with acquired atrial septal defects as complications of combined aortic and mitral valve replacements. Although a transseptal approach to the mitral valve was the most likely cause for the atrial septal defect in 1 patient, the atrial septum was not incised in the second patient. The authors proposed that the atrial septum, because of its proximity to the aortic root, was included in the aortic prosthetic valve suture line, with resulting ischemic necrosis and subsequent slough resulting in an interatrial communication. Roberts and colleagues [9], in a postmortem study of 224 patients who died after cardiac valve replacement, reported a single instance of a small ventricular septal defect created after aortic valve replacement. However, this was considered to be hemodynamically insignificant. Left ventricular–coronary sinus fistulas have been reported following multiple mitral valve replacements [4, 7]. The oximetry data and angiocardiograms must be carefully reviewed to avoid confusing this fistula with a direct left ventricular–right atrial defect. During reexcision of a mitral prosthesis that becomes embedded in the posterior ventricular myocardium, an intramural hematoma can form; it then can rupture into the coronary sinus. Finally, Jupa and Carleton [4] reported an aortico-right ventricular fistula occurring after aortic valve replacement. At the time of their report, the patient was asymptomatic and corrective operation was not contemplated.

Acquired intracardiac left-to-right shunts may cause hemodynamic embarrassment either early or late after prosthetic valve replacement. These shunts must be included in the differential diagnosis of cardiac decompensation after valve operation, particularly if extensive debridement of calcium in the septal area was performed during the operative procedure. Prompt recognition and repair of these shunts is mandatory before the onset of irreversible myocardial dysfunction, which markedly increases the mortality of surgical closure, occurs [3].

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Upper Extremity Gangrene: A Complication of Subclavian Artery Division

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ABSTRACT **Gangrene of the upper extremity is a rare complication following subclavian artery ligation. Two case reports from the 23-year experience at the Hospital for Sick Children are presented. If gangrene is to be eliminated in such cases, early recognition of inadequate limb perfusion is mandatory. A suspicion of inadequate perfusion justifies heparin therapy, and prompt revascularization and fasciotomy must be considered.**

The subclavian artery is commonly used for palliation of children with congenital heart disease. Serious complications seldom occur but can be devastating when they do. A review of the surgical literature since 1944, when Blalock and Park reported the first successful Blalock-Taussig shunt [1], reveals only five reported instances of upper extremity gangrene related to subclavian artery division [3]. Four of these occurred in children undergoing Blalock-Taussig shunts and the other in a young man following anastomosis of the subclavian artery and aorta as treatment for coarctation of the aorta. Recently there has been increased interest in the use of the subclavian artery as an arterioplastic flap in the treatment of coarctation, particularly in the infant [4]. At the Hospital for Sick Children, Toronto, between 1946 when the first Blalock-Taussig procedure was performed there and May, 1979, 936 subclavian–pulmonary artery anastomoses have been created. In another 35 infants and children, the subclavian artery has been used as an arterioplastic flap in treatment of coarctation of the aorta. Thus a total of 971 subclavian arteries have been divided since 1944. During this period, gangrene developed in the extremity supplied by the ligated subclavian artery in 2 patients.

Patient 1

A 4½-year-old boy was admitted in 1961 for treatment of cyanotic heart disease. He had had a known heart murmur since birth, and at catheterization when he was 6 months old, the diagnosis of tetralogy of Fallot was confirmed. He was acyanotic until the age of 3 years. During the six months preceding his admission, increased cyanosis, dyspnea on exertion, and squatting were noted.

At the time of admission, he was moderately cyanotic and had clubbing of the fingers and toes. There was a thrill over the left sternal border and an accompanying Grade 3/6 midsystolic murmur. A right Blalock-Taussig shunt was constructed. The arch anatomy was normal. Details of the operative note show that the vertebral artery was ligated separately, and the remainder of the subclavian artery ligated en masse. The operation was uneventful.

Immediately after operation, a continuous murmur was heard over the right chest and the patient was less cyanotic. The right arm was cool, discolored, and mottled. Capillary filling time was estimated to be one-half that of the opposite upper extremity. During the next 24 hours, edema of the right hand was noted. It is clear from the record that the arm appeared much more ischemic than usual following subclavian artery ligation, and at 24 hours there was concern about limb viability.

A clinical diagnosis of arterial spasm was made, and systemic heparinization was begun. The upper arm was explored and the brachial artery directly injected with heparinized saline solution. Stellate ganglion blockade was

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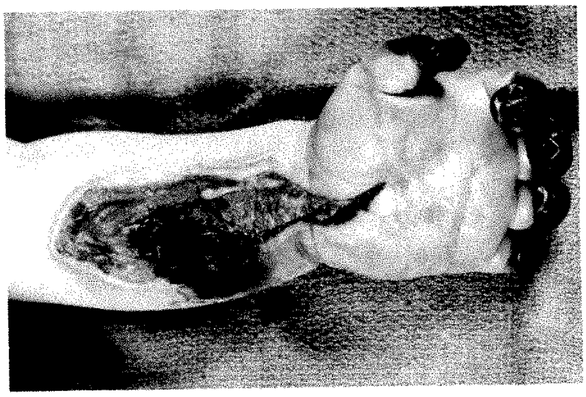
utilized. No improvement was noted and during the ensuing two weeks an edematous gangrene progressed, involving 75% of the forearm. An above-the-elbow amputation was performed thirty-four days after the initial procedure. The patient subsequently underwent uneventful intracardiac repair of tetralogy of Fallot when he was 10 years old.

Patient 2

An asymptomatic 2-year-old boy with coexisting aortic stenosis and coarctation of the aorta underwent cardiac catheterization in December, 1978, and was found to have gradients of 80 mm Hg and 60 mm Hg across the aortic valve and coarctation, respectively. After considerable discussion, it was elected to treat both obstructive lesions simultaneously. With the patient in a modified right lateral decubitus position and with the left arm draped free, a left posterolateral thoracotomy was performed and the coarctation repaired using a subclavian flap arterioplasty as described by Waldhausen and Nahrwold [5]. The branches of the subclavian artery were ligated and divided individually.

Subsequently the arm was placed at the patient's side, and a median sternotomy incision was made. During thirty-four minutes of cardiopulmonary bypass with moderate hypothermia, aortic valvotomy was performed. Following cessation of bypass, protamine sulfate was administered. After closure of the sternotomy incision, the coarctation repair was inspected to ensure good hemostasis. The thoracotomy incision was then closed, and the patient was returned to the intensive care unit. The cardiovascular status remained satisfactory throughout with no evidence of low output syndrome. The immediate postoperative cardiac index was 3.1.

During the first and second postoperative days the left hand was cool but appeared adequately perfused. It should be emphasized that the left upper extremity did not appear different from other upper extremities immediately following subclavian artery ligation. However, on the third postoperative day, the hand was slightly mottled and more cyanotic than before. Motion and sensation were normal. A regimen of heparin was begun to prevent small-vessel thrombosis in the presence of low flow to the extremity. The limb was thought to be viable but more ischemic than usual following subclavian artery ligation. There was no evidence of major muscle ischemia. On the following day, the hand looked better intermittently but was unchanged on the whole. On the fifth postoperative day, there was less spontaneous motion and a question of tenderness over the upper forearm. Edema was lacking to mild. The color was slightly more cyanotic and mottled in the evening.



The child's left arm three weeks following division of the left subclavian artery for coarctation repair. There is dry gangrene of the distal phalanges of all five fingers. The volar fasciotomy wound edges have retracted. The granulation tissue at the base of the wound is healthy except for the central superficial gangrenous area.

On the sixth postoperative day, deep tenderness was present and there was decreased sensation and mobility. A volar forearm and palm fasciotomy and carotid subclavian Gortex graft bypass were performed (5 mm Gortex). Retrograde bleeding from the subclavian arteriotomy was minimal, and pulsation distal to the graft ceased within hours despite complete heparinization. The absence of bleeding from the margins of the fasciotomy was striking. On the evening of the sixth postoperative day, the limb remained ischemic and hyperbaric oxygen therapy was begun (Figure). On May 28, 1979, the fingers were amputated at the distal metacarpals, and the thumb at the proximal phalanx. The remainder of the patient's postoperative course was uneventful. He is normotensive with no pressure gradient between the right brachial and popliteal arteries.

Comment

Ligation of the subclavian artery can be tolerated, even in the adult, without manifest ischemia of the upper extremity. This clinical knowledge was applied with particular emphasis on the treatment of military casualties [2]. Nevertheless, ischemic complications can occur, although their incidence has not been accurately determined. The importance of these 2 patients is that they establish an incidence of 0.2% in a large number of patients seen at a single institution over a 23-year period. The possibility of this complication should be borne in mind with the current trend towards subclavian flap arterioplasty for coarctation repair.

Why upper extremity gangrene following subclavian artery ligation develops in rare instances is unknown. The factors that have been implicated almost certainly do not apply to Patient 1. He had normal arch anatomy, the branches were not ligated individually, the surgeon's prior experience with the procedure was large, and the extremity had not been used for intravenous line placement or otherwise abused. The sequence of events in Patient 2 is more complex. The branches were individually ligated, and this may predispose to ischemia. Also, following ligation the patient underwent cardiopulmonary bypass and cooling, which might greatly have affected perfusion of the ischemic extremity. However, signs of ischemia were not present until the third postoperative day, and this suggests a change in the vascular supply to the limb at that time. The mechanism appeared to be small-vessel thrombosis secondary to poor perfusion from subclavian artery division.

The surgeon must recognize that elective division of the subclavian artery can be followed by catastrophic ischemia of the limb. Appropriate treatment will be effective only if it is begun very early before irreversible changes occur. At the first suspicion of ischemia, the patient should undergo complete heparinization followed by prompt arterial reconstruction and, if necessary, fasciotomy.

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Technique of Mitral Valve Replacement

Marvin M. Kirsh, M.D., and Herbert Sloan, M.D.

ABSTRACT **A technique for mitral valve replacement is described that provides adequate exposure for excision of the valve and secure suturing of the annulus, even in patients with a small left atrium. The technique has been used in more than 100 patients and has resulted in only a minimal amount of perivalvular leak.**

Most cardiac surgeons today perform mitral valve replacement using a median sternotomy incision and a longitudinal left atriotomy just posterior to the interatrial groove. Although we have always been able to perform mitral valve replacement with this incision, there have been times when excision of the valve and suturing of the annulus have been difficult despite the use of ischemic cold potassium arrest. This has usually occurred in patients with a small left atrium. We describe here a technique of mitral valve replacement that provides adequate exposure for excision of the valve and secure suturing of the annulus even in patients with a small left atrium.

Technique

Total cardiopulmonary bypass is established with standard bicaval cannulation techniques using the ascending aorta as the site of cannulation for arterial inflow. A left ventricular vent is inserted through the apex of the heart. The patient is cooled to an esophageal temperature of 28°C. The aorta is cross-clamped and cardiac arrest induced by infusion of cold potassium cardioplegic solution into the aortic root.

The left atrium is opened longitudinally just posterior to the interatrial groove (Figure). Initially the atrial cavity should be examined carefully for thrombus. If present, the thrombus is removed and the orifice of the atrial appendage oversewn. Using a retractor, an assistant pulls the anterior left atrial wall toward the patient's left. Traction is applied to the anterior leaflet with the use of a mitral valve retractor or a stay suture of 1-0 cardiovascular Tevdek passing through its midportion. A No. 11 scalpel is used to make a 1 to 1.5 cm incision in the anterior leaflet midway between the two commissures, parallel to and approximately 2 to 3 mm from the annulus. With continued traction on the leaflet, a double-armed 1-0 Tevdek suture mounted on a 10 × 3 mm Dacron felt pledget is placed through the mitral annulus using a horizontal mattress suture with the pledget on the atrial side of the annulus. The anterior leaflet is sequentially and circumferentially incised to each commissure by the making of four or five 1 to 1.5 cm incisions in the anterior leaflet 2 to 3 mm from the annulus. After each incision, the buttressed mattress suture is placed in the annulus.

Placement of the sutures is facilitated by applying traction on the leaflet away from the annulus. The anterior leaflet is now connected to the papillary muscles only by its chordae tendineae. With right-angle scissors, the tips of the papillary muscles are excised. The surgeon must take care to avoid any undue traction on them. Following this, the posterior leaflet and its adjacent chordae tendineae are excised.

(A) Characteristic appearance of a mitral valve with severe stenosis. (B) Exposure of the valve is facilitated with the use of a stay suture. A 1 to 1.5 cm incision is made in the midportion of the anterior leaflet. (C) With continued traction on the leaflet, one to three Tevdek sutures mounted on pledgets are placed through the mitral annulus. (D) The anterior leaflet is then circumferentially and sequentially incised to each commissure with multiple incisions. After each incision, the buttress mattress suture is placed. The broken line marks the proposed line of excision of the posterior leaflets. (E) Placement of the suture in the posterior leaflet is facilitated by placing traction on the posterior leaflet and countertraction on the previously placed sutures. (F) Placement of the suture in the anterior commissure is provided by applying traction simultaneously to the last sutures placed in the anterior and the posterior annulus.

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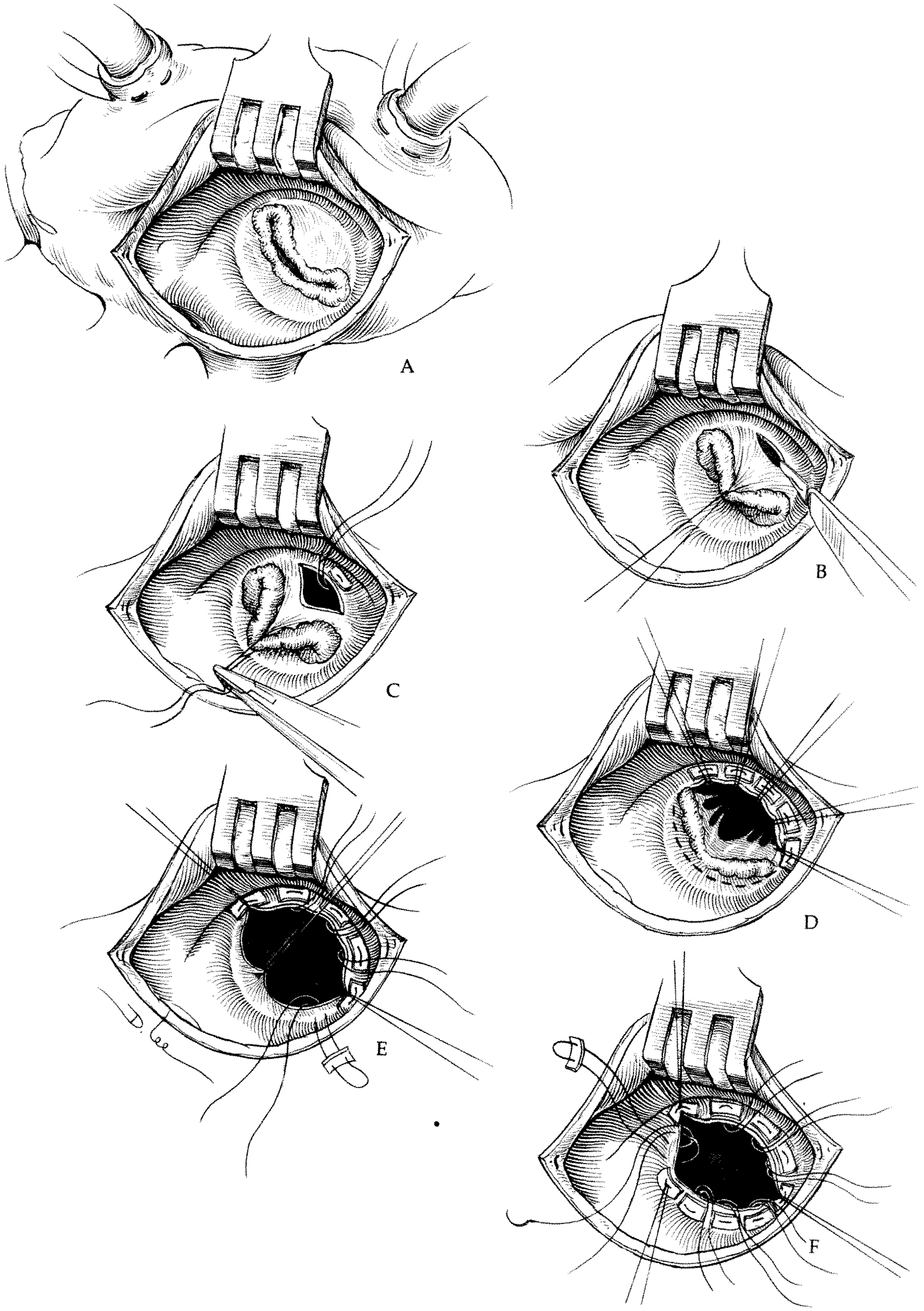
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Suturing of the posterior annulus is begun at the posterior commissure and carried out in a clockwise manner. The edge of the remnant of the posterior leaflet is grasped with a stay suture or a right-angle clamp and retracted away from the annulus. Placement of the sutures in the posterior annulus is facilitated by applying traction on the remnant of the posterior leaflet and countertraction on the previously placed sutures. Exposure of the posterior annulus in the vicinity of the anterior commissure is provided by applying traction simultaneously to the last sutures placed in the anterior and posterior annulus. The sutures are then passed through the sewing ring in a horizontal mattress fashion. After the prosthesis is tied in place, the pledgets are buried beneath the sewing ring of the prosthesis. Usually only ten to twelve sutures are required.

The aortic clamp is removed and as the patient is being rewarmed, the left atriotomy is closed. Care must be taken to avoid air embolization as the patient is being weaned from cardiopulmonary bypass.

Comment

We have used this technique of mitral valve replacement in more than 100 patients over the past several years. Aortic cross-clamp time is generally less than forty-five minutes, the exposure is good, and the incidence of perivalvular leak is minimal.

A New Temporary Pacing Electrode

Francis Robicsek, M.D., Steven A. Robicsek, and Herbert A. Ferrari, M.D.

ABSTRACT **A simple method for the positioning of a temporary pacemaker electrode in the course of open-heart operation is presented. Instead of using "back stitching," we recommend that after the wire electrode is passed through the myocardium, it should be driven through a small pledget of Silastic rubber material to hold it in position.**

Pacing electrode wires are used routinely in the postoperative period in most patients who undergo open-heart operation. They are a simple and effective way of assuring satisfactory heart rate if the patient's own pacing system becomes inadequate.

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The electrodes used for this purpose are usually specially prepared with a curved needle on one end and a straight needle on the other. The curved needle is used to introduce into the myocardium that portion of the pacing wire denuded of insulation, while the other end of the wire is brought through the chest wall and attached to an external pacing device. As a rule, two pacing wires are inserted into either the right or left ventricular myocardium, one used as a negative and the other as a positive electrode. When external pacing or pacing standby is no longer necessary, the wires are simply pulled out from the myocardium by exerting traction on the extrathoracic ends.

While insertion of temporary electrodes is certainly a very simple procedure, problems such as inadvertent removal of the electrode during thoracotomy closure or inappropriate contact between the bare ends of the lead causing loss of pacing often occur. These problems are due primarily to the generally practiced way of electrode attachment to the myocardium, i.e., a simple through-and-through suture with a backstitch of identical depths and lengths placed a few millimeters away. This manner of lead fixation has several disadvantages.

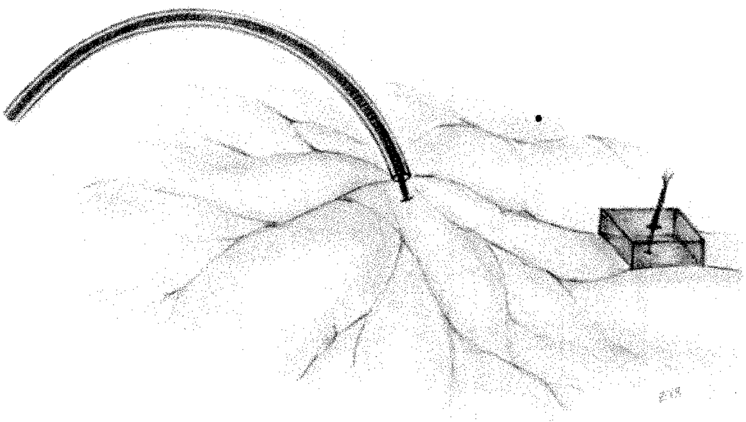

Fig 1. Temporary electrode in position. The uninsulated portion of the wire is passed through the myocardium and then brought through a small Silastic pledget and cut short. The elasticity of the pledget keeps the wire safely in position but does not prevent its removal.

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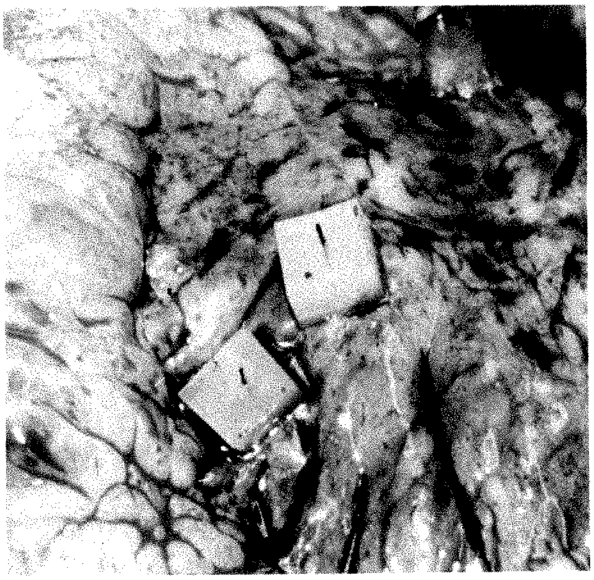

Fig 2. Two temporary pacing electrodes in position (operative site).

1. It is a very unreliable way of electrode insertion. Sometimes the slightest pull is enough to dislodge the electrode. On the other hand, at times the "backstitch" offers too much resistance to removal and could lacerate the heart muscle.
2. The free end of the wire electrode must be a minimum of 3 to 4 mm long to protrude from the myocardium. Thus, it can touch the other electrode inadvertently and short the circuit.
3. The "bare" terminal portion of the electrode has nearly the same diameter as the insulated portion. This makes pulling of the insulated part into the myocardium easy and could lead to loss of pacing.

Modification

To eliminate these disadvantages, we made some simple modifications on the presently commercially available temporary pacemaker leads. The terminal end of the insulating coating was thickened, thereby minimizing the possibility of inadvertently pulling it into the myocardium. Fixation of the lead to the myocardium was changed by eliminating the backstitch and by driving the curved swedged-on needle after its passage through the ventricular wall through a small pledget of silicone rubber 3 mm in diameter (Fig 1). The pledget is pushed down to the epicardial surface, and the rest of the wire protruding from the pledget is cut short. This arrangement provides a much firmer fixation of the electrode wire to the myocardium and still allows a smooth disengagement at the time of removal of the electrode (Fig 2). The small, biologically entirely inert silicone pledget simply stays in the pericardial cavity after removal of the temporary electrode.

Comment

This method was used successfully in 50 patients following open-heart operation. There were no complications.

Obstruction of the True Lumen during Retrograde Perfusion of Type I Aortic Dissections: A Simplified Solution

Grant V. S. Parr, M.D., Norman J. Manley, B.S., C.C.P.,
Dennis R. Williams, C.C.P., and Ralph M. Montesano, C.C.P.

ABSTRACT **Retrograde perfusion of the false lumen in cases of type I dissection of the thoracic aorta may not permit reperfusion of the coronary arteries when the aortic cross-clamp is removed. We have employed a Y connector between the coronary perfusion outlet of the oxygenator and cardioplegia delivery system. This allows reperfusion of the coronary arteries through the ascending aortic graft. As cardiopulmonary bypass is discontinued, the true aortic lumen is reexpanded and the false lumen collapsed by forward flow of blood from the heart. The successful use of this system is described.**

The common femoral artery is the preferred site of arterial cannulation for repair [1] of DeBakey type I aortic dissections [3]. Retrograde perfusion may be through the true or false aortic lumen, depending on the way the dissection reenters (Fig 1). Perfusion of the false lumen is a problem not only of inadequate renal or cerebral perfusion, but also of possible inadequate reperfusion of the heart when the aortic cross-clamp is removed. In this situation, after resection of the entrance tear in the intima of the ascending aorta, the false lumen is closed between the prosthetic graft and a reinforcing strip, often Teflon felt. The aortic intima forms a flap valve, and there can be no blood flow back to the heart (Fig 2A).

Technique

Replacement of the perfusion cannula in the ascending aorta has been recommended for retrograde aortic dissection [2]. We prefer not to do this because it requires discontinuing cardiopulmonary bypass and then placing a large cannula in the ascending aortic graft. We have modified our standard cardioplegia infusion apparatus with a simple Y connector placed between the coronary perfusion outlet of the oxygenator and the cardioplegia infusion line (Fig 3). When cardioplegia is being induced, a pump clamp is placed at point A on one limb of the Y. If it is necessary to reperfuse the heart, the clamp is moved from point A to point B on the other limb of the Y. The cardioplegic solution is flushed into a basin. A single coronary perfusion cannula is then placed in the ascending aorta and the heart may be reperfused while the aortic cross-clamp remains in place (Fig 2B). After the heart has begun to beat well, the ventricular vent is removed. Cardiac ejection should be noted on the manometer. The perfusion cannula is then converted to an aortic vent, and the cross-clamp may be removed. As the heart ejects, the true lumen is opened and the false lumen collapses (Fig 2C). Cardiopulmonary bypass may then be discontinued in the usual fashion.

Case Report

A 63-year-old woman was admitted to another hospital on November 27, 1978, with chest and left leg pain. The left femoral pulse was absent. Subsequently a diastolic murmur and signs of pericardial tamponade developed. Pericardiocentesis improved her hemodynamic state transiently. She was transferred to the Milton S. Hershey Medical Center while continuous pericardiocentesis was performed, with the aspirate being reinfused into a central venous line.

On admission, the patient was intubated and comatose, and had a blood pressure of 50 mm

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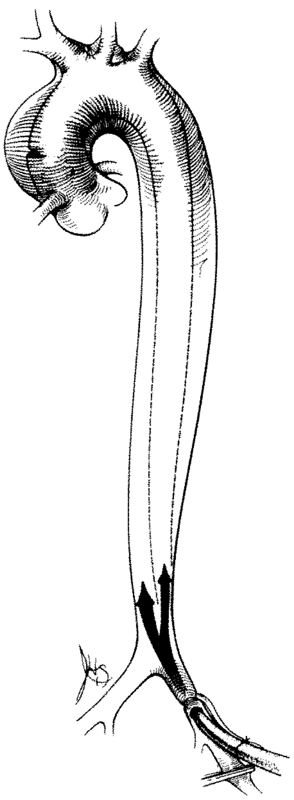

Fig 1. *Retrograde femoral perfusion of a type I aortic dissection may be through the true or false lumen.*

Hg systolic. We did not believe she would survive long enough to allow an aortogram, and thus she was taken promptly to an operating room where a pump oxygenator with an asanguineous prime had been prepared. The patient was rapidly prepared, draped, and heparinized, and the right common femoral artery was cannulated under local anesthesia. Only then was anesthesia induced and a sternotomy performed. Pericardiotomy yielded profuse bleeding, which was removed by the pump suckers. A single venous cannula was inserted, and full bypass was then established. The site of bleeding was identified as the atrioventricular grove anteriorly, presumably from dissection down the right coronary artery. A left ventricular vent was advanced through a pursestring suture in the left atrium near the right superior pulmonary vein. The heart was profoundly cooled by the perfusate and when the ventricle fibrillated, the aorta was cross-clamped and the perfusate temperature set at 24°C. The aorta was opened, and 1,200 ml of cold potassium cardioplegic solution was infused into the coronary ostia until the ventricular septal temperature was 10°C. Examination showed a type I dissection with dissection into all aortic sinuses and a large dissection along the right coronary artery. The aortic valve could not be repaired and was replaced with a 23 mm Björk-Shiley prosthesis.

An additional 500 ml of cold potassium cardioplegic solution was then infused into the coronary arteries. A proximal anastomosis was constructed between the supracoronary part of the aorta and a 30 mm woven Dacron tube graft using a running horizontal mattress suture of 3-0 polypropylene monofilament suture buttressed with a strip of Teflon felt. Rewarming was begun while a distal anastomosis closed the false lumen. The intima and the adventitia were buttressed by the Dacron graft and by a Teflon felt strip, respectively (see Fig 2A).

When the aortic cross-clamp was removed, the graft remained flaccid. Retrograde flow through the false lumen was recognized, and the cross-clamp was replaced. The pump clamp was removed from point A in Figure 3 and replaced at point B. The cardioplegic solution was flushed from the circuit, and a single coronary perfusion cannula was placed into the ascending aortic graft through a pursestring suture. After several minutes, the heart was electrically defibrillated. The left ventricular vent was removed, and the ventricular ejection was seen in the manometer on top of the cardioplegic bubble trap. The cross-clamp was removed after 75 minutes, and the ventricle was found to eject. The coronary perfusion cannula was connected into a vent for evacuating air as cardiopulmonary bypass was gradually discontinued. During this period, the true lumen had reexpanded and the false lumen had collapsed. Additional suturing was necessary in the area of the right coronary artery.

The postoperative course was prolonged by respiratory insufficiency (perhaps secondary to the preoperative infusion of pericardial blood into the central venous line) and a transient left hemiparesis. The latter may have been due to air embolus after bypass or to preoperative or intraoperative occlusion of the innominate artery by the false lumen. The patient was discharged on the fifty-seventh day.

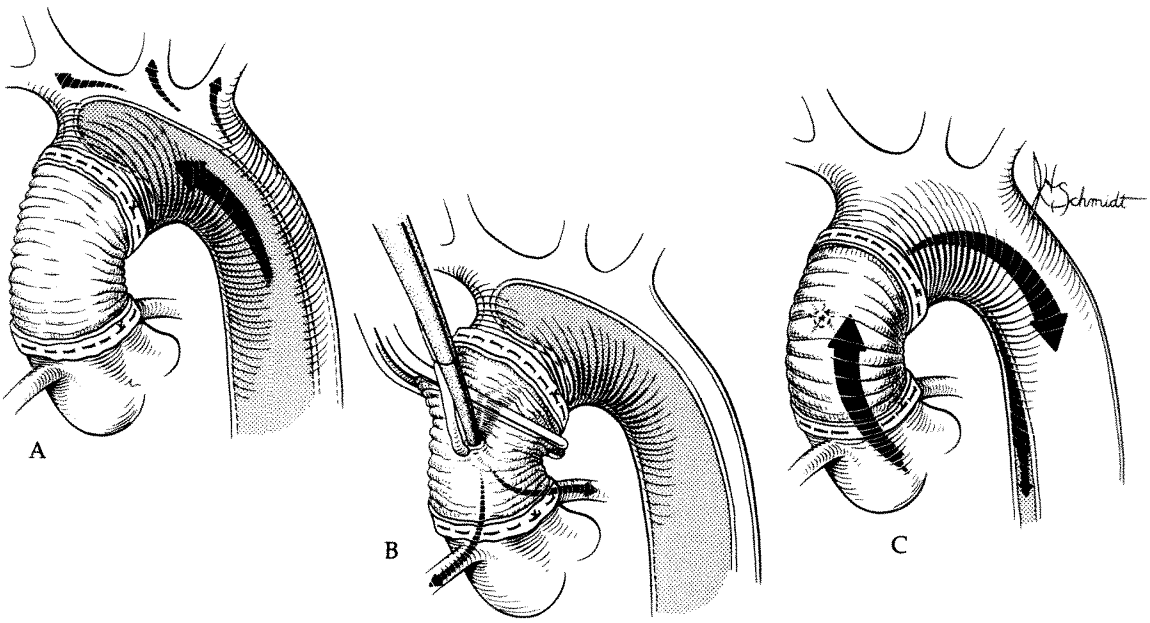

Fig 2. (A) Retrograde perfusion of the false lumen (shaded) can raise a flap of intima, which will obstruct the true lumen (unshaded). The false lumen is closed between the graft and a Teflon felt strip obstructing reperfusion of the coronary arteries. (B) Reperfusion of the coronary arteries through a cannula in the ascending aortic graft. (C) When the heart ejects, the false lumen (shaded) is collapsed and the true lumen is reexpanded.

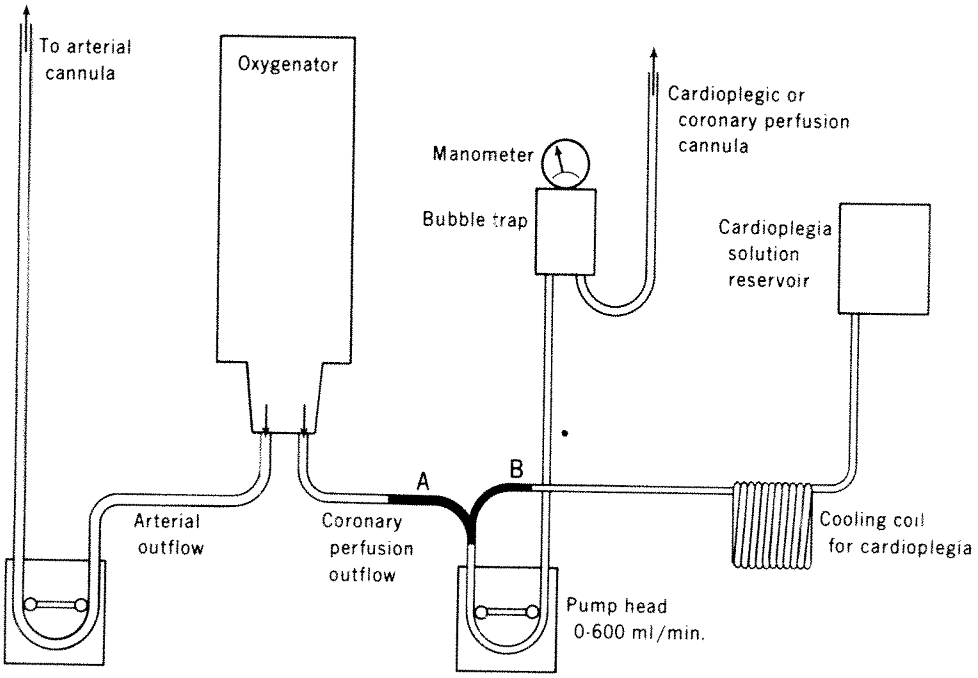
To arterial cannula
Oxygenator
Manometer
Bubble trap
Cardioplegic or coronary perfusion cannula
Cardioplegia solution reservoir
A
B
Arterial outflow
Coronary perfusion outflow
Cooling coil for cardioplegia
Pump head 0-600 ml/min.

Fig 3. A Y connector is inserted between the coronary perfusion outlet and the cardioplegia delivery system. When a clamp is removed from point A and placed at point B, oxygenated blood may be delivered.

Comment

Retrograde perfusion of the false lumen in cases of type I dissections of the aorta is not infrequent. Retrograde dissections have also been recognized from femoral artery cannulation with other cardiac disease [2]. We now routinely modify our perfusion setup as described, in all instances where femoral artery cannulation is planned. The system is inexpensive (about $3.00 additional cost) and effective. The simplicity of the system allows for immediate implementation of cardiac reperfusion without the need to disrupt perfusion to the body.

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COLLECTIVE REVIEW

The Surgical Treatment of Ventricular Tachycardia

Alden H. Harken, M.D., Leonard N. Horowitz, M.D.,
and Mark E. Josephson, M.D.

ABSTRACT **Recurrent ventricular tachycardia is a well-recognized complication of ischemic heart disease. Coronary bypass operation with or without aneurysmectomy has been disappointing as therapy for these arrhythmias. With the advent of programmed electrical stimulation, it has become possible to distinguish automatic and reentrant ventricular tachyarrhythmias. The latter have recently proved amenable to operative intervention.**

This review examines the pathophysiology and diagnosis of ventricular tachycardia using programmed electrical stimulation. Surgical therapy with resection, revascularization, autonomic modulation, thermal ablation, cardiac pacing, reentrant circuit interruption, and endocardial excision is explored. Operation for cardiac arrhythmias is on a firm electrophysiological foundation. Surgical treatment of refractory ventricular tachyarrhythmias is now rational, recommended, and rewarding.

The mechanism of ventricular tachycardia is enhanced automatically, reentrant, or a combination of both [33, 65, 67, 75]. Automatic ventricular tachycardia is common in the perioperative and periinfarction periods. Reentrant ventricular tachycardia is most frequently associated with chronic ischemic heart disease. Operation has proved feasible only for reentrant ventricular tachycardia. Currently, there is no evidence to support a surgical approach to automatic ventricular tachycardia and no reason to operate for isolated premature ventricular contractions. The purpose of this review is to explore the rationale and results of operation for ventricular tachycardia.

Reentrant Arrhythmias

Mechanism

More than fifty years ago, Wenckebach and Winterberg [71] postulated reentry as a mechanism for ventricular arrhythmias. In order for reentry to occur, two or more electrically heterogeneous (with respect to conduction and refractoriness) pathways must be connected proximally and distally [42, 65]. An impulse must travel in only one direction along one of these pathways (unidirectional block). If this impulse arrives at the distal connection, it may return by the originally blocked pathway. If conduction of the impulse is sufficiently slow to allow the initially blocked site to recover excitability, the impulse may reenter the circuit. The requirements for such a reentrant mechanism are [51, 65]: (1) unidirectional block, (2) slow conduction over an alternative route, (3) delayed excitation just distal to the blocked tissue, and (4) reexcitation of the proximal tissue upon return of the impulse. These reentrant precursors have been documented in cardiac muscle strips [5, 51, 74] and intact dog heart [8, 10]. Examination of arrhythmia mechanisms was not feasible in the human heart until Durrer and Roos [9] developed the technique of programmed electrical stimulation.

Programmed Stimulation

The techniques of programmed ventricular stimulation include rapid ventricular pacing and the introduction of progressively premature ventricular stimuli during sinus rhythm or ventricular pacing [33]. A premature ventricular depolarization is initially introduced in late diastole (Figs 1, 2) and then progressively earlier until no ventricular response is elicited (ventricular refractoriness). If this fails to induce ventricular tachycardia, then double premature stimuli are introduced with the second stimulus introduced beginning 50 to 100 msec longer than the effective ventricular refractory period. This sequence is repeated until ven-

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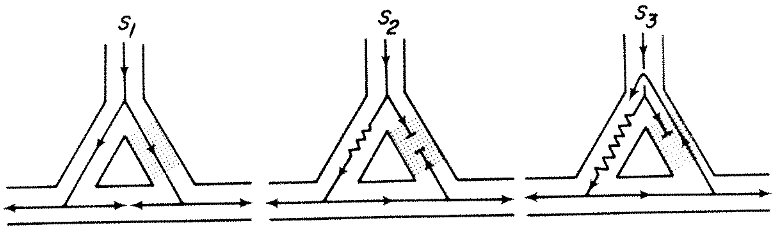


Fig 1. Schema for reentry: S_1*,* S_2*, and* S_3 *represent paced premature depolarizations. An area of ventricle capable of reentry is depicted in each panel. In* S_1*, the depolarization wave front proceeds down both limbs of the diseased circuit. With a second (*S_2*) paced premature ventricular depolarization (PVD), the wave front travels down the left limb slowly* (sawtooth line) *but its return in the right limb is blocked. With a third PVD (*S_3*), conduction proceeds even more slowly down the left limb (slow conduction) and is blocked in the right limb (undirectional block). In this instance, conduction down the left limb is sufficiently slow to permit repolarization of the pathological* (stippled area) *right limb. The wave front therefore returns along the right limb and reexcites the origin to reenter the circuit.*

tricular tachycardia is initiated. Once ventricular tachycardia is induced, programmed single, double, and triple ventricular stimuli are introduced in an attempt to terminate the arrhythmia [33].

Induction of ventricular tachycardia by programmed stimulation is taken as evidence supporting reentry as the mechanism for the arrhythmia. The reasoning is as follows: During programmed stimulation, at a critical coupling interval one pathway (see Fig 1) in the reentrant circuit becomes blocked (unidirectional block) and the activation wave front proceeds exclusively along the other arm of the circuit [65]. After traversing one pathway, the impulse returns along the previously blocked portion of the circuit and reexcites (or reenters) the original pathway. In vitro studies [75] have demonstrated that rapid pacing can result in rate-dependent block in depressed segments of Purkinje tissue, thus providing both conditions for reentry. El-Sherif and co-workers [12, 13] have demonstrated pacing-induced fragmentation of impulse wave fronts in the postinfarction heart with variably depressed conduction leading to reentrant ventricular arrhythmias. Indeed, slow response activity and the substrates for reentrant rhythms have been initiated and documented in human ventricular aneurysm tissue excised at operation [55].

Therefore, it is understandable how a premature ventricular depolarization occurring at just the critical time might establish a reentrant rhythm in diseased myocardium. In contrast, paced premature beats have no influence on ventricular tachycardia due to a hyperexcitable automatic focus since slow conduction and altered refractoriness are not related to its genesis. Thus, inducibility of a ventricular arrhythmia is accepted as evidence for a reentrant mechanism. This rule, however, does not appear to be absolute, for under specific experimental conditions, abnormal automaticity due to enhanced afterpotentials has been induced by paced premature stimulation [7, 15, 67, 73]. Operationally, however, an inducible tachycardia is considered reentrant [7, 67]. As a prerequisite to surgical therapy, an arrhythmia must be inducible (and therefore probably reentrant) to permit preoperative and intraoperative localization. In contrast, a focal automatic ventricular tachycardia should respond nicely to surgical ablation. The problem is finding the focus. The arrhythmia is not (by definition) inducible and therefore typically not present in the catheterization laboratory or operating room for precise localization (mapping).

Therapy

Ventricular tachycardia must be inducible (therefore reentrant) in order to permit intraoperative mapping and surgical repair. If a ventricular tachycardia is reentrant, it seems logical that effective therapy should require only interruption of the reentrant circuit rather than complete surgical excision. This concept is appealing for no surgeon is eager to excise more ventricle than is absolutely necessary.

Ventricular Resection and Revascularization

The incidence of postinfarction ventricular tachyarrhythmias has been reported to be as

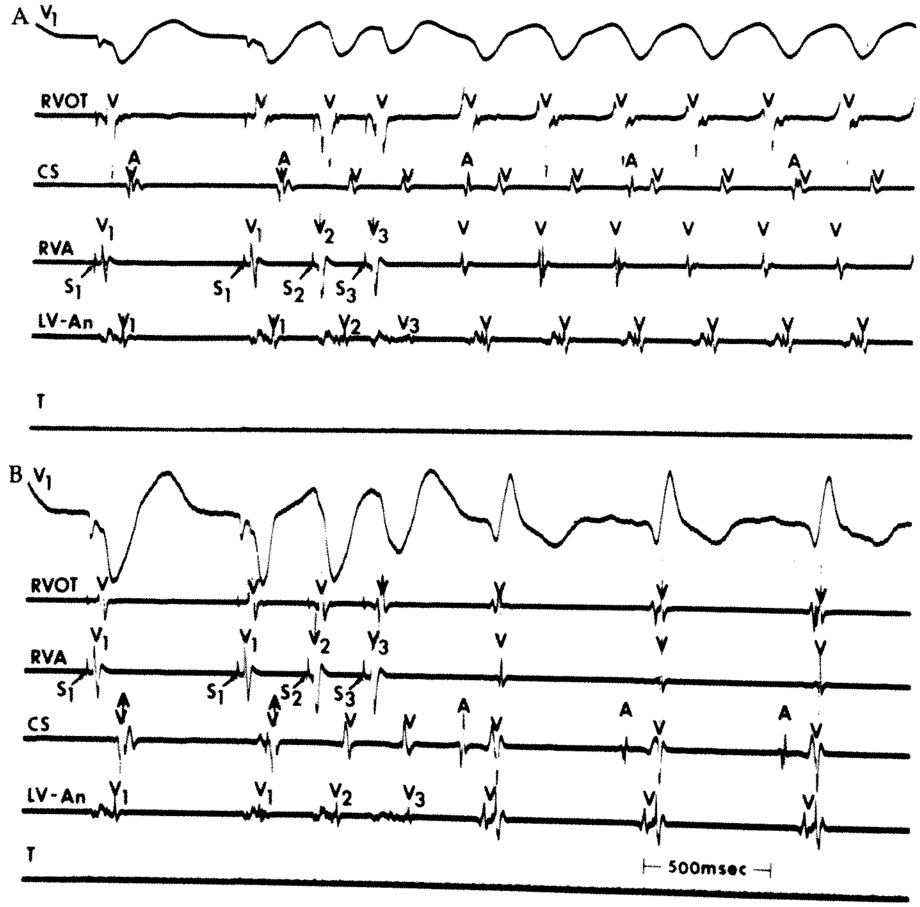


Fig 2. (A) Preoperative and (B) postoperative endocardial catheter mapping. Programmed premature ventricular depolarizations (S_1, S_2, S_3) are introduced at the right ventricular apex (RVA). *Precordial lead V_1 and endocardial electrograms in the right ventricular outflow tract* (RVOT), *coronary sinus* (CS), *and left ventricular aneurysm* (LV-AN) *are monitored. Atrial* (A) *and ventricular* (V) *depolarizations are identified. Prior to surgical endocardial excision, programmed premature depolarizations (S_1, S_2, S_3) induced sustained ventricular tachycardia. Following operation, programmed ventricular stimuli (S_1, S_2, S_3) captured the ventricle, but the mechanism reverted to sinus rhythm when the programmed stimuli were stopped. The programmed premature depolarizations (S_1, S_2, S_3) depicted here correspond to the diagrams of S_1, S_2, and S_3 in Figure 1.*

high as 80% [6, 38, 40]. Prior to effective medical therapy, recurrent postinfarction ventricular tachycardia was associated with a mortality as high as 67% [1]. Although medical management has improved, coronary artery disease continues to afflict people in the United States. Since angina responds so nicely to revascularization and resection, it was hoped that these procedures might also correct the factors predisposing to postinfarction ventricular tachyarrhythmias. When aortocoronary bypass and infarctectomy have been performed within four to six weeks of myocardial infarction, mortality has been high. In a group of 7 such patients, Mundth and associates [45] had 3 deaths, with ventricular tachycardia persisting in 1 of the survivors. Ricks and co-workers [48] reported an 80% mortality in this "acute" group. Mortality fell to 20% in the nonacute group, and many patients survived despite persistent ventricular arrhythmias. Waxman and colleagues [64] resected and revascularized 14 patients with intractable ventricular tachycardia an average of four weeks after infarction and achieved a 50% 3- to 12-month survival. These patients are sick, however, for 6 similar patients treated medically in this series [64] died within a week of discharge. Several groups [3, 11, 24, 34, 60, 72] have reported necessarily limited series with some unequivocally successful results. It is not clear in these cases whether success was achieved due to improved blood supply and improved ventricular function or whether a reentrant circuit was fortuitously caught in the ventricular suture line. As surgical management has improved, remarkable operative salvage has been achieved. Revascularization and simple ventricular resection have yielded suboptimal results in eliminating ventricular tachycardia. Sami and associates [50] resected and revascularized 10 patients with recurrent ventricular tachycardia without a death. Two of the patients died suddenly at 1.5 and 7 months, presumably of recurrent arrhythmias, and 3 of the survivors have documented ventricular tachycardia. This surgically successful but electrophysiologically frustrated group [50] concluded that aneurysmectomy does not abolish ventricular tachyarrhythmias.

Autonomic Modulation

Traditionally, ventricular tachycardia is recognized as unresponsive to vagal traffic while supraventricular tachycardias are slowed or converted by parasympathetic stimulation [36]. Waxman and associates [62, 63], however, have reported termination of ventricular tachycardia in 12 patients by phenylephrine and convincingly associated this with parasympathetic activity.

Conversely, sympathectomy has been used to reduce the incidence of ventricular arrhythmias associated with experimental myocardial infarction in animals [28, 52]. Complete cardiac sympathectomy requires excision of the ganglia from the stellate down through the seventh thoracic level bilaterally [21, 52], necessitating access to both thoracic cavities. In 1961, Estes and Iziar [14] reported success in the treatment of ventricular tachycardia in humans with cardiac sympathectomy. Subsequent groups have used sympathectomy in conjunction with other modalities. Zipes and co-workers [76] successfully combined atrial pacing with sympathectomy in 1 patient. Similarly, Lloyd and associates [37] found that cardiac sympathectomy permitted the medical control of ventricular tachycardia previously refractory to propranolol.

Cardiac sympathectomy may improve conditions and permit adjunctive control of ventricular tachyarrhythmias, but typically is inadequate as the sole method of control. Nitter-Hauge and Storstein [46] applied sympathectomy in 5 patients with refractory ventricular tachycardia, and achieved complete control in 2 and temporary control in 1. This is a reasonably characteristic batting average; Sealy and Oldham [54] reported successful arrhythmia control in up to 58% of patients following cardiac sympathectomy.

Thermal Ablation

The trepidation associated with ventricular resection seems directly related to the volume of normal muscle excised. For this reason, techniques of disrupting a reentrant circuit without destroying anatomical and perhaps even functional myocardial integrity have particular appeal. Gallagher and associates [22, 23, 29] have described a cryosurgical technique not requiring cardiopulmonary bypass for the controlled ablation of selected myocardial tissue. Also, this group [35] has examined the cryosurgical lesion in dogs and noted that it heals by fibrosis into a firm scar that does not disrupt surrounding tissue. This inert plug of scar does not influence surrounding transmural or epicardial activation. Induced ventricular ectopic activity about the cryolesion does not persist beyond one week. Cryoablation has been used successfully to treat ventricular tachycardia [22]. In this instance, the site of tachycardia origin was located and cooled to 0°C with prompt termination of the arrhythmia. Further cooling to −60°C resulted in irreversible ablation of the focus. In this manner, the circuit may be diagnostically disrupted prior to irreversible ablation. This technique does depend on highly precise localization of the tachycardia origin. It may also require the reentrant circuit to follow an epicardial course along at least a portion of its route. In 1979, Camm and colleagues [4] successfully treated ventricular tachycardia with cryosurgery and cardiopulmonary bypass. Cryoablation of a site on the interventricular septum was performed through a right ventriculotomy. The patient was free from ventricular tachycardia after 6 months of follow-up.

Electrocautery is perhaps a similar but opposite method of disrupting the reentrant circuit. This technique also has been used effectively in the treatment of refractory ventricular tachycardia [47].

Cardiac Pacing

Wellens and associates [65, 67, 70] have suggested that reentrant ventricular tachycardia should be able to be reproducibly initiated and terminated by programmed stimulation. For reentry to occur, the relation between the velocity of the excitatory wave front and the duration of the refractory period is critical [68]. Therefore, it ought to be feasible to disrupt this precisely timed reentrant circuitry with bursts of rapid ventricular pacing. The paced impulses should extinguish the reentrant tachycardia by colliding with the reentering wave front. Alternatively, this paced wave front should also invade the reentrant circuit, thereby creating refractoriness ahead of the circulating impulse responsible for the arrhythmia. Both mechanisms of disrupting the finely tuned reentrant circuitry should work. Application of implanted pacemakers for the control of arrhythmias is relatively new. Although the use of a demand pacemaker for competitive pacing seems paradoxical [49], magnetically activated ventricular pacemakers have been implanted and used successfully to control ventricular tachycardia [2, 17, 20, 66].

The problems associated with pacing therapy, however, are both those of difficulty and danger. The site of ventricular stimulation that terminates the tachycardia may be tough to find and difficult to chronically attach with an endocardial pacing lead [43, 64]. The potential for ultimately disorganizing the ventricular rhythm into fibrillation also exists. Interestingly, even this apparent disaster is within the frontiers of bioengineering manipulation. An implantable low-energy demand defibrillator with a transvenous catheter electrode system has been developed [41, 44]. Wide application of this innovative concept requires further work, however.

Reentrant Circuit Interruption

Wellens and co-workers [70] have suggested large reentrant circuits that might include the bundle branches, Purkinje fibers, adjacent muscle, and infarcted ventricular tissue. Precise delineation of the conduction pathways comprising a reentrant circuit have yet to be precisely delineated [12, 53]. If macro-reentry is indeed the mechanism of the typical recurrent postinfarction ventricular tachycardia, then precisely placed ventricular incision rather than resection might effectively interrupt the circuit and terminate the tachycardia.

In 1974, Guiraudon and colleagues [27] reported the successful treatment of refractory ventricular tachycardia with an appropriately placed 4 to 5 cm transmural ventricular incision. Subsequently, this group [19] has mapped the arrhythmia and incised the ventricle of 6 patients with nonischemic ventricular tachycardia. Two patients died on the fifth and eighth days following operation, and the rest have been free from arrhythmias for up to four years [18]. Similar operative localization and ventriculotomy techniques have been used by Spurrell and co-workers [57–59] with similar results.

Fontaine and colleagues [18] operated on 7 patients with ventricular tachycardia due to cardiomyopathy and 13 patients with postinfarction ventricular tachycardia, and found late potentials in all patients with cardiomyopathy and successfully terminated the arrhythmia with a ventriculotomy in each instance. However, in the patients with postinfarction ventricular tachycardia, they generated "uninterpretable data" in 11 of 13 and were successful in surgically terminating the arrhythmia in only 1 patient.

More recently, Guiraudon and associates [26] performed a nontransmural, encircling ventriculotomy in 5 patients with medically refractory, ischemic ventricular tachycardia. This procedure (Fig 3) involves opening the ventricle through the area of infarction. A nontransmural ventriculotomy is performed perpendicular to the wall (or septum) at the junction between the aneurysmal scar and normal myocardium. The incision is repaired with a running suture. This technique is based on the premise that the reentrant circuit arises in the border zone between normal and scarred tissue. The ventriculotomy is intended to interrupt the reentrant pathway. All 5 patients reported [25] survived the operation and are arrhythmia-free

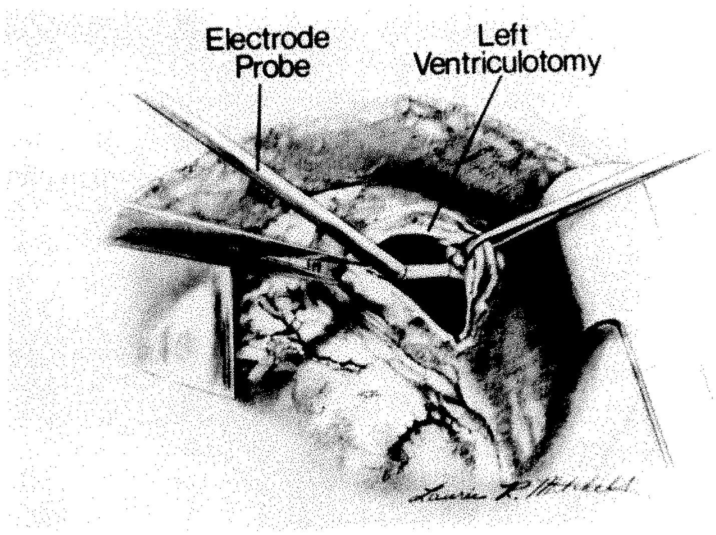


Fig 3. Endocardial mapping: The left ventricle is entered through the aneurysm. The endocardium is then mapped circumferentially at 1 cm levels out from the aneurysmal edge. This mapping is performed during sustained ventricular tachycardia. The earliest site of ventricular activation during ventricular tachycardia is shown.

6 to 24 months following operation. These results are encouraging, and this procedure is intuitively logical for macro-reentrant ventricular tachyarrhythmias in which the circuit can be confined to a discrete anatomical site.

Endocardial Excision

Using programmed stimulation and endocardial catheter mapping, Josephson and colleagues [31] have demonstrated that ventricular tachycardia is due to a relatively protected focal reentrant circuit. Spielman and associates [56] have documented the limitations of epicardial mapping in localizing the origin of focal ventricular tachycardia in a canine model. They also documented sites of epicardial breakthrough 5 mm to 6 cm distant from the endocardial site of tachycardia origin. In addition, Josephson and associates [33] have documented two distinct ventricular tachycardia morphologies in 14 of 26 patients studied in the electrophysiology laboratory. Endocardial mapping indicates that both morphologies derived from the same endocardial origin with different reentrant circuits and epicardial sites of breakthrough. It does not appear to be necessary therefore to ablate a separate site for each tachycardia morphology. Surgically, it is essential only to destroy the origin. This evidence perhaps explains the disappointing results with nondirected surgical therapy of ventricular arrhythmias [39, 61]. Although automatic and reentrant ventricular tachycardia may potentially coexist in the same patient [21], the arrhythmia is reproducibly inducible only if reentry is the mechanism. Operationally, therefore, electrophysiological evalulation of drug therapy and mapping before and during operation is feasible only with reentrant arrhythmias.

A logical approach to this group of ventricular tachycardias would appear to necessitate directed operation guided by programmed stimulation and mapping. Josephson and associates [30] have recently reported encouraging results with electrophysiologically directed surgical excision of the tachycardia origin. They documented 12 patients with postinfarction ventricular tachycardia as medically refractory. At operation, reference electrodes are placed in normal left and right ventricle. Ventricular tachycardia is induced with programmed stimulation. An epicardial map is performed. This typically takes 20 to 30 minutes depending on the ease with which ventricular tachycardia is initiated. The ventricle is opened through the area of infarction. An endocardial map is performed. A ref-

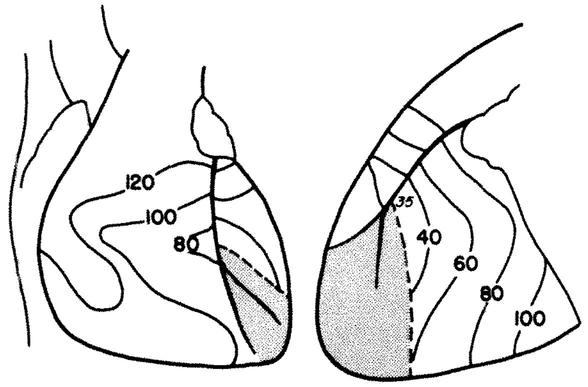
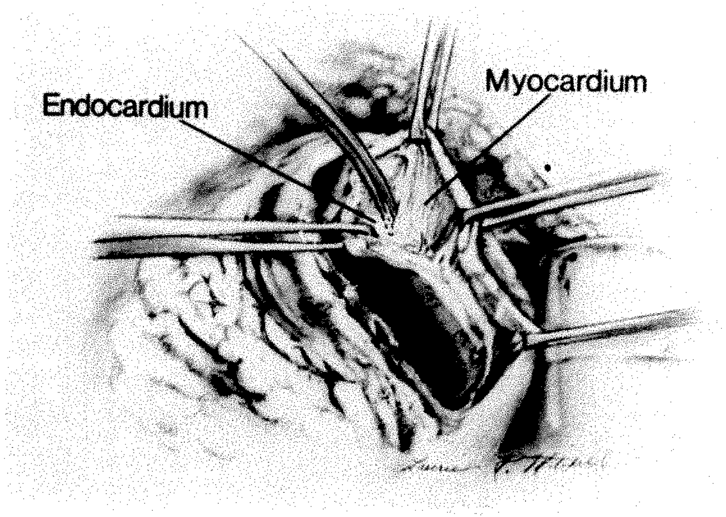


Fig 4. An isochronous map made at operation of the anterior and lateral epicardial surfaces. The stippled area represents palpable left ventricular aneurysm. Earliest epicardial breakthrough occurred at the aneurysmal edge on the lateral heart surface 35 msec following the QRS interval measured on the endocardium.

erence electrode site is arbitrarily defined as zero time. The tachycardia QRS interval at each epicardial and endocardial site is then assigned a time either later (+msec) or earlier (−msec) than the reference site. An isochronous map (Fig 4) is constructed. The earliest site (characteristically on the endocardium) is defined as the tachycardia origin. A peel of endocardium is then excised (Fig 5) 2 to 3 cm back from the ventriculotomy (or aneurysmectomy) edge and encompassing one-third of the ventricular circumference. There has been 1 operative (twenty-four hours) and 1 late (six weeks) death. All patients were electrically studied (see Fig 2) following operation and in no instance was the ventricular arrhythmia inducible with programmed stimulation off all antiarrhythmic medications. This electrically directed surgical ablation has rewarded appealing logic with gratifying results.

Fig 5. Endocardial excision: The left ventricle is entered through the aneurysm or area of infarction. An endocardial peel (free wall or septum) is then excised 2 to 3 cm back from the ventriculotomy (or aneurysmectomy) edge and encompassing one-third of the ventricular circumference.



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FIFTEENTH POSTGRADUATE PROGRAM
THE SOCIETY OF THORACIC SURGEONS

Sunday, January 25, 1981
Los Angeles Bonaventure, Los Angeles, CA

Morning Session

8:00 Introduction to the 1981 Postgraduate Course
Robert W. M. Frater, Bronx, NY

I. Survey of Chest Trauma

Moderators J. Kent Trinkle, San Antonio, TX
Robert W. M. Frater, Bronx, NY

8:10 Diaphragmatic, Esophageal, and Tracheobronchial Injuries
Tom R. DeMeester, Chicago, IL

8:35 Chest Wall Fractures, Flail Chest, and Pulmonary Contusion: New Therapeutic Approaches
J. Kent Trinkle, San Antonio, TX

9:00 Blunt and Penetrating Heart Wounds
Melvin R. Platt, Dallas, TX

9:25 Aortic and Other Large Vessel Injuries
Edward J. Hurley, San Diego, CA

10:10 Panel discussion and questions

II. Myocardial Metabolism and the Surgeon

Moderator Daniel J. Ullyot, San Francisco, CA

11:00 Speaker: James Scheuer, New York, NY

11:45 Questions and discussion

12:00 Lunch

Afternoon Session

III. Hyperalimentation in Cardiac, Esophageal, and Pulmonary Disease

Moderator Edward J. Hurley, San Diego, CA

1:00 Speaker: M. Terry McEnany, Columbus, OH

1:45 Panel discussion and questions

IV. Which Valve Should I Use?

Moderators L. Henry Edmunds, Jr., Philadelphia, PA
Robert W. M. Frater, Bronx, NY

2:00 Thromboembolic Incidence Compared
L. Henry Edmunds, Jr., Philadelphia, PA

2:20 Durability Compared
Daniel J. Ullyot, San Francisco, CA

2:40 Hemodynamics Compared
Robert W. M. Frater, Bronx, NY

3:00 Composite Comparison
The Panelists

3:30 Panel discussion and questions

V. The Mediastinum: Developments, Controversies, and Illumination

3:55 New Concepts in the Pathophysiology of Myasthenia Gravis
Tom R. DeMeester, Chicago, IL

4:00 Thymectomy by the Suprasternal Route
Joel Cooper, Toronto, Ont, Canada

4:10 Thymectomy by the Transsternal Route
Alfred Jaretzki, III, New York, NY

4:20 Looking at the Mediastinum by Computerized Axial Tomography
Ralph Alfidi, Cleveland, OH

4:40 Panel discussion and questions

This program is sponsored by the Committee on Postgraduate Education of The Society of Thoracic Surgeons in conjunction with the Seventeenth Annual Meeting.

Registration ($35 fee includes luncheon) is open to all thoracic surgeons and residents. Details regarding registration will be mailed to members; others should write to the Secretary, W. Gerald Rainer, M.D., The Society of Thoracic Surgeons, 111 E Wacker Dr, Chicago, IL 60601.

This program is authorized for eight hours of Category I CME credit.

PROGRAM
FOR SEVENTEENTH ANNUAL MEETING OF THE SOCIETY OF THORACIC SURGEONS

January 26–28, 1981
Los Angeles Bonaventure, Los Angeles, CA

January 26, 1981 (Monday)
Morning

8:00 Business Meeting (members only)

8:15–12:00 **Scientific Session**

1. Ultimate Prognosis after Valve Replacement: An Assessment at Twenty Years
Joseph F. Teply, Gary L. Grunkemeier, and Albert Starr, Portland, OR

2. Ten-Year Follow-up in Aortic Valve Replacement Using the Björk-Shiley Prosthesis
David Cheung, Donald C. Mullen, Robert J. Flemma, and Derward Lepley, Jr., Milwaukee, WI

3. Mitral Valve Replacement with the Hancock Bioprosthesis: Five- to Ten-Year Follow-up
A. Michael Borkon, Charles L. McIntosh, Lewis C. Lipson, Thomas J. Von Rueden, Stephen E. Epstein, and Andrew G. Morrow, Bethesda, MD

4. Medium-Term Follow-up of Ionescu-Shiley Heterograft Valve
Ronald M. Becker, Lawrence Sandor, Michael Tindel, and Robert W. M. Frater, Bronx, NY

5. Primary Reconstruction of Airway after Resection of Subglottic Laryngeal and Upper Tracheal Stenosis
Hermes C. Grillo, Boston, MA

6. High-Frequency Jet Ventilation in Major Airway or Pulmonary Disruption: Clinical Experience
Alan D. Turnbull, Graziano C. Carlon, William S. Howland, and Edward J. Beattie, New York, NY

7. Massive Hemoptysis: Control by Transcatheter Bronchial Artery Embolization
Donald J. Magilligan, Jr., Pierre Zayat, Seetaramaiah Ravipati, and Puranchander Shetty, Detroit, MI

8. Diagnosis and Long-Term Follow-up of Major Bronchial Disruptions Due to Nonpenetrating Trauma
Jean Deslauriers, Maurice Beaulieu, Gaétan Archambault, and Jacques LaForge, Ste-Foy, Que, Canada

Afternoon

1:30–5:00 **Scientific Session**

9. Surgical Treatment of Ventricular Tachycardia Guided by Ventricular Mapping in Twenty-four Patients
Gerard Guiraudon, Guy Fontaine, Robert Frank, Jean Barra, and Christian Cabrol, Paris, France

10. His Bundle Interruption for Control of Inappropriate Ventricular Responses to Atrial Arrhythmias
Will C. Sealy, John J. Gallagher, and Jackie Kasell, Durham, NC

11. Clinical Experience with Permanent Atrioventricular Sequential Pacing
Jack J. Curtis, Niall P. Madigan, Richard B. Whiting, Karl J. Mueller, A. Thomas Pezzella, and Fred M. Heinemann, Columbia, MO

12. Manual Coronary Endarterectomy with Saphenous Bypass: Experience with 263 Patients
Eugene Wallsh, Andrew J. Franzone, Roy H. Clauss, Ciro Armellini, and Simon H. Stertzer, New York, NY

13. Aggressive Treatment of Acquired Phrenic Nerve Paralysis in Infants and Small Children
Robert Shoemaker, G. Palmer, John W. Brown, and Harold King, Indianapolis, IN

14. Prospective Evaluation of Four Methods of Lung Biopsy in Patients with Diffuse Pulmonary Infiltrates
Michael E. Burt, Bruce L. Weber, Robert A. Wesley, and M. Wayne Flye, Bethesda, MD

15. Fine Needle Aspiration Biopsy in the Diagnosis of Lung Lesions
T. R. J. Todd, J. D. Cooper, W. Cass, R. Ilves, N. C. Delarue, and F. G. Pearson, Toronto, Ont, Canada

16. Site of Recurrence in Patients with Stages I and II Carcinoma of the Lung Resected for Cure
Steve C. Immerman, Robert M. Vanecko, Willard A. Fry, Louis R. Head, and Thomas W. Shields, Chicago, IL

17. Mediastinoscopy in Advanced Superior Vena Caval Obstruction
Ralph J. Lewis, Glenn E. Sisler, and James W. MacKenzie, Piscataway, NJ

Evening

8:30–10:00 **Surgical Motion Pictures**

Moderators: Joel Cooper, Toronto, Ont, Canada, and Andrew S. Wechsler, Durham, NC

1. Apical Left Ventricular–Aortic Bypass: A Method for Relief of Left Ventricular Outflow Obstruction
Russ Zajtchuk, Bethesda, MD

2. The Transsternal Approach to Tracheal Resection
Tom R. DeMeester, Chicago, IL

3. Renal Cell Carcinoma Extending into Inferior Vena Cava and Right Atrium: Surgical Technique Employing Cardiopulmonary Bypass, Profound Hypothermia, and Total Circulatory Arrest
John R. McCormick, Boston, MA

4. Plexectomy and Coronary Bypass for Variant Angina
Hooshang Bolooki, Miami, FL

5. The Heterotopic Heart Transplant
Donald R. Kahn, Birmingham, AL

6. Femoroperoneal Bypass: Fibulectomy Approach
Wade C. Lamberth, Jr., Iowa City, IA

January 27, 1981 (Tuesday)
Morning

7:00–8:00 **Breakfast Sessions—Problem Case Presentations**
(see pp 515–516 for program)

8:15–11:30 **Scientific Session**

18. Ligation of Patent Ductus Arteriosus in Premature Infants
B. Brandt, III, W. J. Marvin, J. L. Ehrenhaft, Sharon Heintz, and D. B. Doty, Iowa City, IA

19. Early Experience with Arterial Repair of Transposition
William Williams, Robert Freedom, Gordon Culham, Walter Duncan, Peter Olley, Richard Rowe, and George Trusler, Toronto, Ont, Canada

20. Coarctation of the Aorta in Children: Twenty-five Years' Experience
David B. Lerberg, Robert L. Hardesty, Ralph D. Siewers, and Henry T. Bahnson, Pittsburgh, PA

21. Experience with Left Ventricular Apicoaortic Conduits for Complicated Left Ventricular Outflow Obstruction in Children and Young Adults
M. Arisan Ergin, Rubin Cooper, Michael LaCorte, Richard Golinko, and Randall B. Griepp, Brooklyn, NY

22. Porcine Valve Longevity in Children
Jeffrey Marc Dunn, Philadelphia, PA

23. Is the Length of Aortic Occlusion with Cold K^+ Cardioplegia a Major Factor in Cardiac Mortality and Morbidity in Coronary Bypass Surgical Patients?
Syed T. Raza, G. Schimert, T. Z. Lajos, A. B. Lee, J. N. Bhayana, B. McCluskey, and J. H. Siegel, Buffalo, NY

24. Comparison of Dopamine and Dobutamine following Coronary Artery Bypass Grafting
Neal W. Salomon, John Plachetka, and Jack G. Copeland, Tucson, AZ

11:30–12:00 **Presidential Address**
Jay L. Ankeney

Afternoon

1:30–3:00 **Forum Session**

25. Blunt Chest Trauma: Clinical Significance of Isolated First Rib Fracture
Edward S. Yee, Arthur N. Thomas, and Philip C. Goodman, San Francisco, CA

26. Fluosol-DA, an Artificial Blood for Total Cardiopulmonary Bypass
Richard M. Engelman, John H. Rousou, and William A. Dobbs, Springfield, MA

27. Laser Endoscopy
Richard B. McElvein, Birmingham, AL

28. Cold Blood Diltiazem Cardioplegia
Hendrick B. Barner, Max Jellinek, John W. Standeven, Leo J. Menz, and John W. Hahn, St. Louis, MO

29. A Clinically Relevant Canine Lung Cancer Model: Six-Year Report
John R. Benfield, Edwin C. Shors, William G. Hammond, Rao P. Paladugu, Arthur H. Cohen, Paul C. Fu, Hyun Y. Pak, and Raymond L. Teplitz, Duarte, CA

30. Harmful Effects of Ventricular Distention during Postischemic Reperfusion
Scott K. Lucas, Hartzell V. Schaff, John T. Flaherty, Vincent L. Gott, and Timothy J. Gardner, Baltimore, MD

31. Mechanical and Cellular Bacterial Clearance in Lung Atelectasis
Davis C. Drinkwater, Carin Wittnich, David S. Mulder, and Ray C. J. Chiu, Montreal, Que, Canada

32. Transmural Gradient in High-Energy Phosphate Content in Patients with Coronary Artery Disease
Robert N. Jones, Robert B. Peyton, Edward W. Holmes, Judith L. Swain, Richard L. Sabina, Peter Van Trigt, Thomas L. Spray, and Andrew S. Wechsler, Durham, NC

33. Limitations of Potassium Cardioplegia during Cardiac Ischemic Arrest: A ^{31}P Nuclear Magnetic Resonance Study
Philippe Menasche, Anne Catherine Pernot, Joanne S. Ingwall, Michel Bercot, Armand Piwnica, and Eric T. Fossel, Paris, France

34. Pharmacological Modification of Spinal Cord Ischemia in the Dog
William A. Nylander, Jr., John W. Hammon, Jr., Edward Oldfield, Robert Plunkett, and William F. Meacham, Nashville, TN

3:30–5:00 Business Meeting (members only)

Evening **The President's Evening**
Tour of Universal Studios, Reception, and Dinner

January 28, 1981 (Wednesday)
Morning

7:00–8:00 **Breakfast Sessions—The Clinical Workshops**
(see p 516 for workshops)

8:30–12:30 **Scientific Session**

35. Perforations of the Esophagus from Gunshot Wounds
Julio Popovsky, Cleveland, OH

36. Colon Interposition for Advanced Nonmalignant Esophageal Stricture: Experience with 40 Patients
Kamal A. Mansour, Henry A. Hansen, II, Theodore Hersh, Joseph I. Miller, Jr., and Charles R. Hatcher, Jr., Atlanta, GA

37. Hypothermic Circulatory Arrest for Resection of Aortic Arch Aneurysm
Denton A. Cooley, David A. Ott, Aldemir Coelho, and O. Howard Frazier, Houston, TX

38. Surgical Treatment of Ruptured Aneurysm of the Aortic Sinuses
Pan-Chih, Cao Qing-heng, Chen-Chun, and Liu Jie-fu, Shanghai, People's Republic of China

39. Repair of Large Chest Wall Defects: Experience with Twenty-two Patients
H. Eschapasse, J. Gaillard, E. Henry, G. Fournial, F. Berthoumieu, and X. Desprez, Toulouse, France

40. Immediate Reconstruction of Full-Thickness Chest Wall Defects
Arthur D. Boyd, William W. Shaw, Joseph G. McCarthy, Daniel C. Baker, Naresh K. Trehan, Anthony J. Acinapura, and Frank C. Spencer, New York, NY

41. Emergency Room Thoracotomy for Resuscitation of "Fatal" Penetrating Injuries of the Heart
R. Ivatury, P. Shah, K. Ito, G. Ramirez, and M. Rohman, Bronx, NY

42. Emergency Thoracotomy in the Surgical Intensive Care Unit after Open Cardiac Operation
Ronald M. Fairman and L. Henry Edmunds, Jr., Philadelphia, PA

43. Secondary Sternal Closure following Open-Heart Operation
I. Gielchinsky, Mark Silidker, Bhaktan Krishnan, and Victor Parsonnet, Newark, NJ

January 27, 1981 (Tuesday)
First Breakfast Session

Session Committee: Andrew S. Wechsler, Durham, NC, and Lazar J. Greenfield, Richmond, VA

7:00–8:00 PROBLEM CASE PRESENTATIONS*
(Simultaneous Sessions)

SEMINAR I
TRACHEOBRONCHIAL PROBLEMS

Discussant: Hermes C. Grillo, Boston, MA

Case Presentations

1. Resection of Left Lung and Carina at Simultaneous Bilateral Thoracotomy
   Dov Weissberg, Holon, Israel
2. Total Replacement of the Trachea
   Jean Deslauriers, Maurice Beaulieu, and Pierre Corriveau, Ste-Foy, Que, Canada
3. Hemoptysis in Endobronchial Metastasis
   Reinold J. Jones and John Rondano, San Francisco, CA

SEMINAR II
THORACIC TRAUMA: AORTIC INJURY

Discussant: Lawrence H. Cohn, Boston, MA

Case Presentations

4. Traumatic Aortic Dissection with Multiple Areas of Rupture
   Ronald M. Becker, Bronx, NY
5. Ruptured Thoracic Aortic Aneurysm in a Jehovah's Witness
   John H. Rousou and Richard M. Engelman, Springfield, MA

SEMINAR III
ACQUIRED TRACHEOESOPHAGEAL FISTULA

Discussant: F. G. Pearson, Toronto, Ont, Canada

Case Presentations

6. Traumatic Tracheoesophageal Fistula
   Robert L. Mullin, New Haven, CT
7. Blunt Esophageal Rupture and Repair of Esophageal Fistula
   Aaron Lucas, Anna Lee Adams, Gordon R. Tobin, Lewis M. Flint, Jr., Norman Snow, and Laman A. Gray, Jr., Louisville, KY
8. Tracheobronchial Fistula after Lye Ingestion
   Robert J. Ginsberg, Toronto, Ont, Canada

SEMINAR IV
CONGENITAL HEART PROBLEMS

Discussant: George G. Lindesmith, Los Angeles, CA

Case Presentations

9. Pulmonary Valvular Atresia, Ventricular Septal Defect, and Very Small Pulmonary Arteries
   Timothy J. Gardner, Baltimore, MD
10. Pulmonary Artery Sling
    Robert D. Brickman, Donald Nuss, David H. Johnson, and Thomas Rubio, Norfolk, VA
11. Truncus Arteriosus with a Pulmonary Artery Sling
    David S. Kastl, Grant V. S. Parr, and John A. Waldhausen, Hershey, PA

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*No advance registration. Attendance by ticket only and restricted to 32 individuals per seminar. Tickets can be purchased at registration desk beginning Sunday at noon and will include breakfast and seminar.

SEMINAR V

PULMONARY-MEDIASTINAL PROBLEMS

Discussant: Kenneth L. Mattox, Houston, TX

Case Presentations

12. Hemorrhagic Pulmonary Infarction Complicating Delayed Bullet Embolectomy
    William I. Brenner, Daniel B. Frost, and Victor A. Silberman, Los Angeles, CA
13. Surgical Management of Neoplasm of the Thymus
    James A. Gibbons, San Diego, CA
14. Right Lower Lobe Cavity and Probable Active Pulmonary Tuberculosis of Right Upper Lobe
    Porter Mayo and Sibu P. Saha, Lexington, KY

SEMINAR VI

ADULT CARDIAC PROBLEMS

Discussant: John L. Ochsner, New Orleans, LA

Case Presentations

15. The Umbilical Vein for Myocardial Revascularization
    Gary M. Silver, F. L. Stutzman, Newell E. Wood, Louis C. Zanger, Gordon E. Katske, and Leonard P. Krajewski, San Jose, CA
16. Massive Aortic Insufficiency with Recurrent Ventricular Fibrillation following Prosthetic Valve Endocarditis
    Agustin Arbulu and Ingida Asfaw, Detroit, MI

January 28, 1981 (Wednesday)
Second Breakfast Session

Session Committee: Joel D. Cooper, Toronto, Ont, Canada, and Eldred D. Mundth, Philadelphia, PA

7:00–8:00 THE CLINICAL WORKSHOPS*

(Simultaneous Sessions)

WORKSHOP I

INDICATIONS AND TECHNIQUES FOR ESOPHAGEAL REPLACEMENT

Discussion Leader: Raymond Postlethwaite, Durham, NC

WORKSHOP II

BRONCHOSCOPIC TECHNIQUES

Discussion Leader: L. Penfield Faber, Chicago, IL

WORKSHOP III

CURRENT METHODS FOR REPAIR OF CHEST WALL DEFECTS

Discussion Leaders: Peter C. Pairolero and P. G. Arnold, Rochester, MN

WORKSHOP IV

SURGICAL APPROACHES TO ANEURYSMS OF THE AORTIC ARCH

Discussion Leader: Denton A. Cooley, Houston, TX

WORKSHOP V

OPERATION FOR POSTINFARCTION VENTRICULAR SEPTAL DEFECT

Discussion Leader: Willard Daggett, Boston, MA

WORKSHOP VI

MANAGEMENT OF POSTOPERATIVE LOW-OUTPUT STATES

Discussion Leader: John C. Norman, Houston, TX

---

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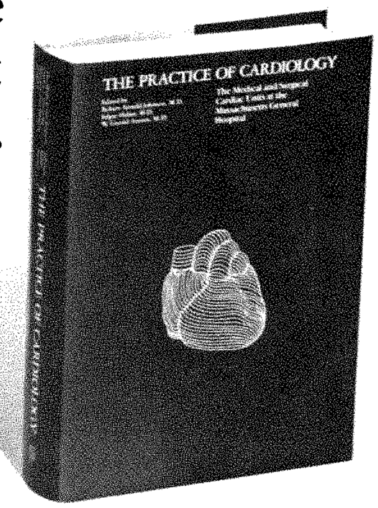

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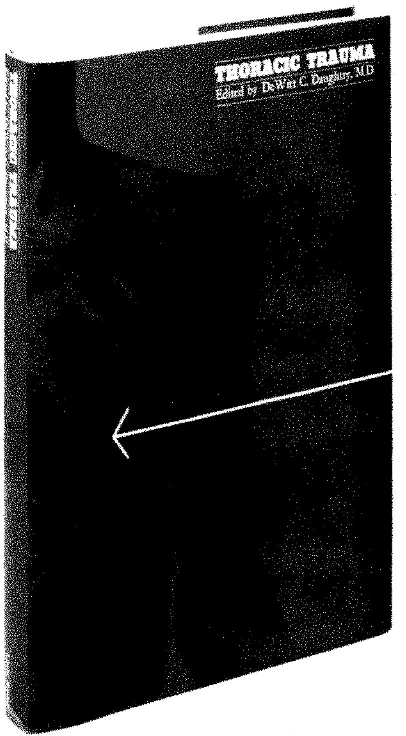

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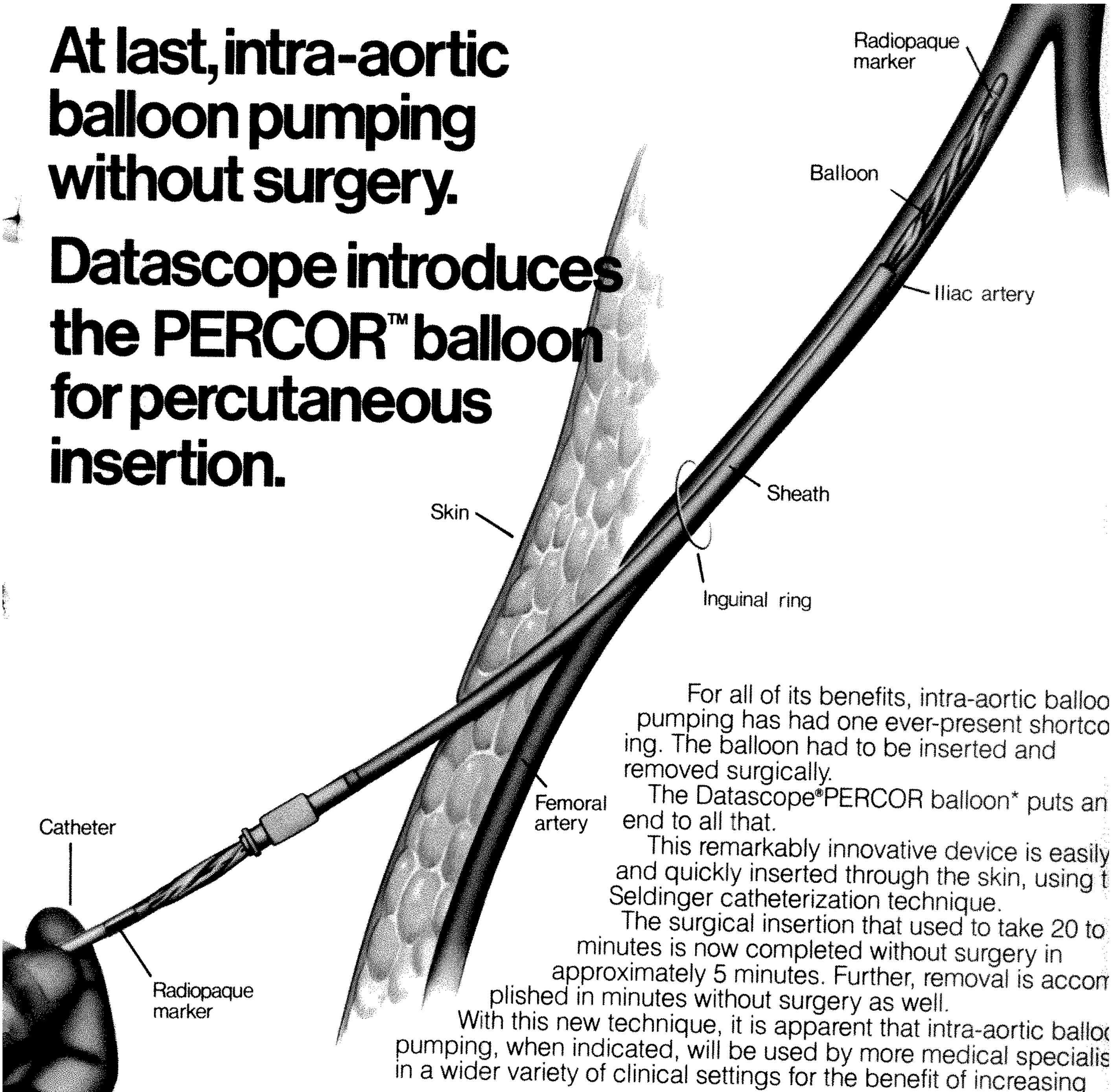

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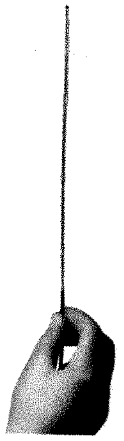

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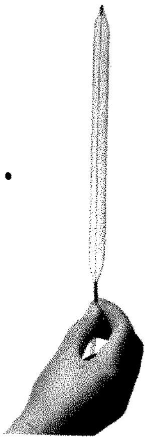

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Cardiovascular and thoracic surgeon, 34, ABS, ABTS, university trained, presently at major university medical center, wishes to enter private practice or relocate to another teaching program. Experienced in adult and pediatric cardiac, thoracic, and vascular surgery. Will consider all locations. CV and operative experience available upon request.

Please respond to W-238, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon, 38, university trained, ABS, ABTS certified, desires position in private practice. Currently associate professor in active university program. Extensive experience in cardiac, thoracic, and vascular surgery. Prefers Northeast or upper Midwest. Curriculum vitae upon request.

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Cardiothoracic surgeon, 33, ABS certified, ABTS eligible, major university hospital–trained in all aspects of thoracic and cardiac surgery. No geographical preference. Seeks faculty position or association with private group. Available July, 1981.

Please respond to W-241, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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Cardiovascular and thoracic surgeon, university trained, ABS certified, ABTS eligible, presently in full-time academic position, seeks to relocate. Would prefer solo or multispecialty group, but will also consider faculty position or association with private group. No geographical preference.

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Chief resident, cardiothoracic surgery, 30, completing busy accredited program in leading university medical center seeks private practice, July, 1981. Academic offers welcomed. Operative experience in large trauma facility, balanced with intense adult-pediatric cardiac, pulmonary, and esophageal services.

Please respond to Mike Brothers, M.D., 308 Robinhood Dr, Irving, TX 75061; tel: (214) 259-6164 or (214) 688-3568.

Thoracic and cardiovascular surgeon, ABTS eligible, 1980 graduate of university residency program, desires to join cardiothoracic surgery group or establish new open-heart program.

Please respond to W-245, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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Please respond to W-246, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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Associate sought in private practice limited to cardiac, thoracic, and peripheral vascular surgery. Rural area in Midwest. Practice expanding rapidly. ABTS required.

Please respond to David S. Starr, M.D., 1393 Mt. Everett, Hubbard, OH 44425; tel: (216) 568-7433.

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Reply with curriculum vitae to A-207, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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Please respond to A-213, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Thoracic surgical group in suburban Boston **seeks new associate,** ABTS certified or eligible.

Submit resume and CV to A-214, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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Please respond to A-219, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiothoracic and vascular surgeon wanted to join thoracic surgeon in group located in upper Midwest Great Lakes community. Must be ABTS certified or eligible. Would prefer someone interested in living in this area.

Please respond to A-220, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgeon associate needed to join very active private practice of adult cardiac and vascular surgery. Large Midwestern metropolitan area. Board-certification or eligibility and university-training required.

Please respond to A-222, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

The Department of Surgery of The Medical College of Pennsylvania, Philadelphia, PA, **invites applications for faculty position in cardiothoracic surgery.** Prefers applications from current senior residents in approved cardiothoracic programs.

Direct inquiries and CV to James O. Finnegan, M.D., Chief, Division of Cardiothoracic Surgery, The Medical College of Pennsylvania, 3300 Henry Ave, Philadelphia, PA 19129.

Academic position for cardiothoracic surgeon available in Northeast. Experience in adult cardiac and thoracic surgery and research required. Attractive terms.

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Please respond with CV to A-226, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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Send CV to A-227, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Surgeon wanted as surgical assistant for active cardiothoracic and vascular group in Pacific Northwest.

Please send resume to A-228, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Excellent opportunity to join active private practice limited to thoracic, peripheral vascular, esophageal, and pacemaker surgery. Noninvasive vascular diagnostic laboratory, no cardiac surgery, Medically sophisticated, beautiful suburb of Washington, DC. ABTS certified or candidate.

Please respond with CV to A-229, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Expanding multispecialty clinic in central Connecticut **seeks thoracic-vascular surgeon,** Board certified or eligible.

Please send CV to A-230, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

Cardiovascular and thoracic surgery fellowship available beginning **July 1, 1981,** in university-affiliated center. Very active clinical program.

Please respond to Chairman, Department of Thoracic and Cardiovascular Surgery, White Memorial Medical Center, 1720 Brooklyn Ave, Los Angeles, CA 90033.

MEETING ANNOUNCEMENT

Thoracic Surgery: A Specialty Review, Dec 1–5, 1980. Sidney Levitsky, M.D., Course Coordinator. AMA Category I Credit: 45 Hours.

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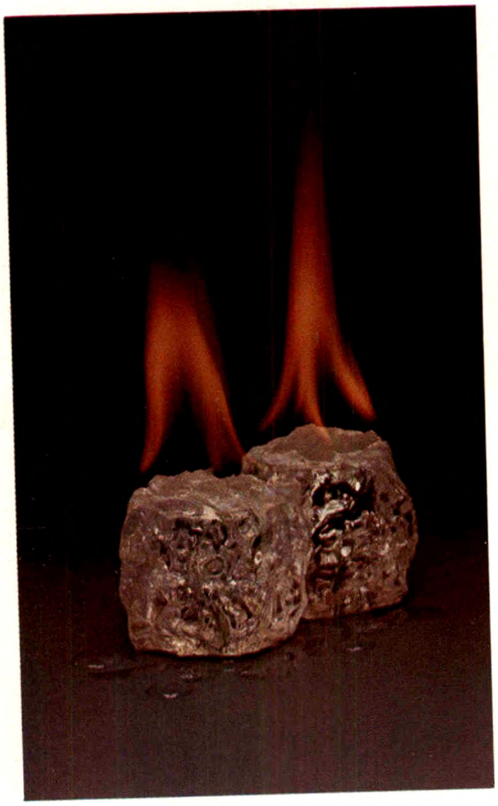

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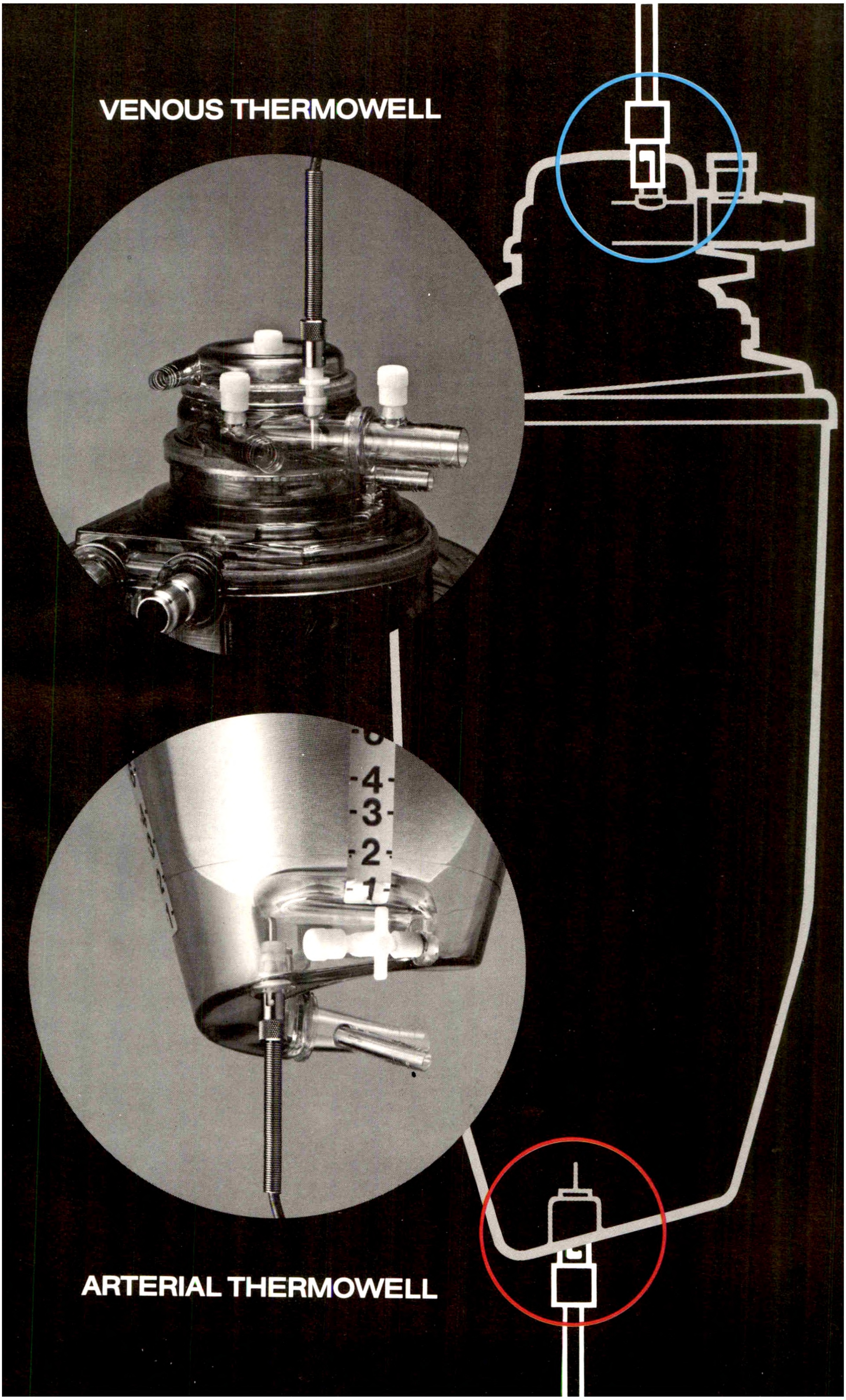
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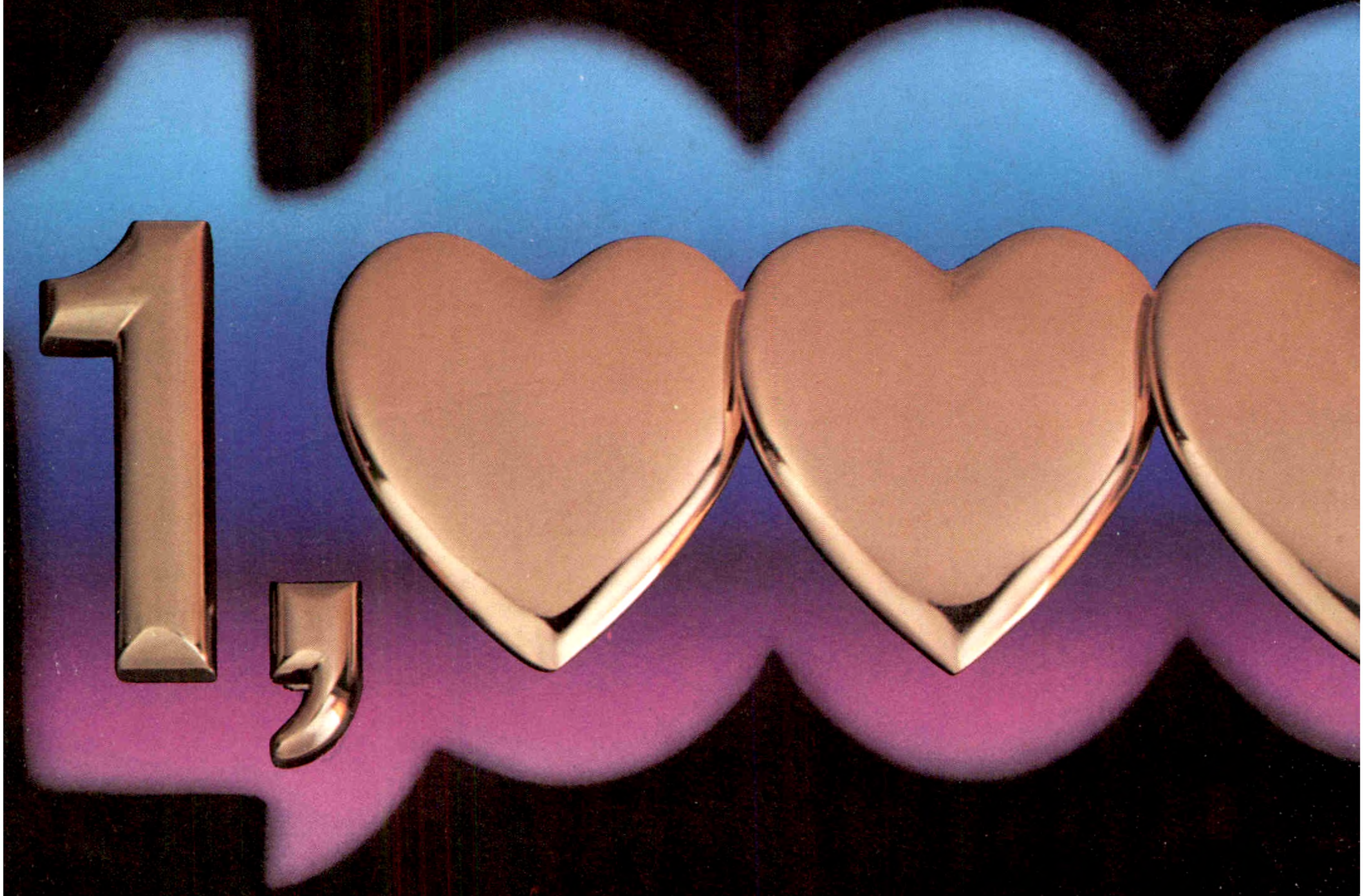

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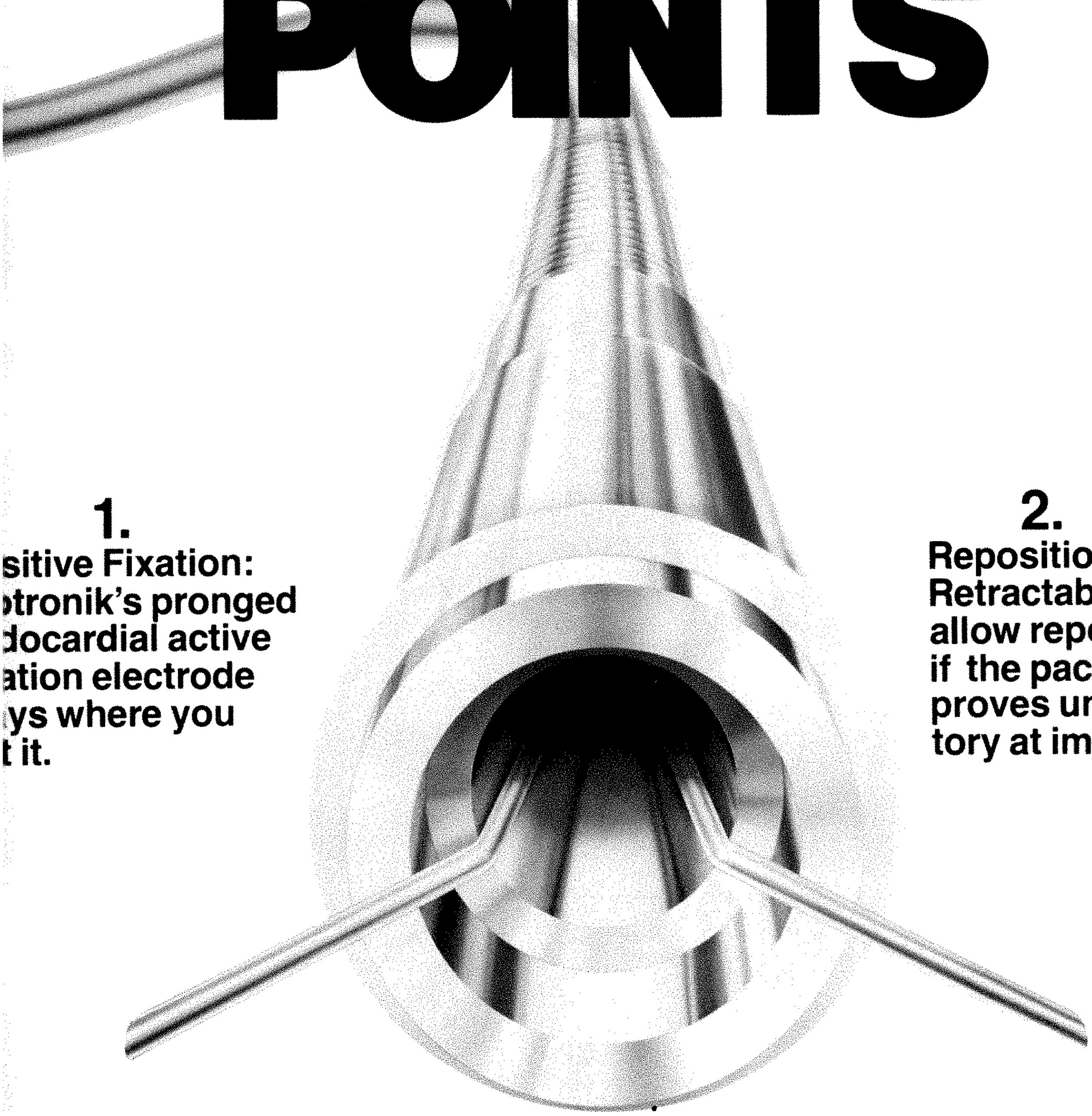

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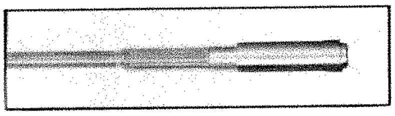

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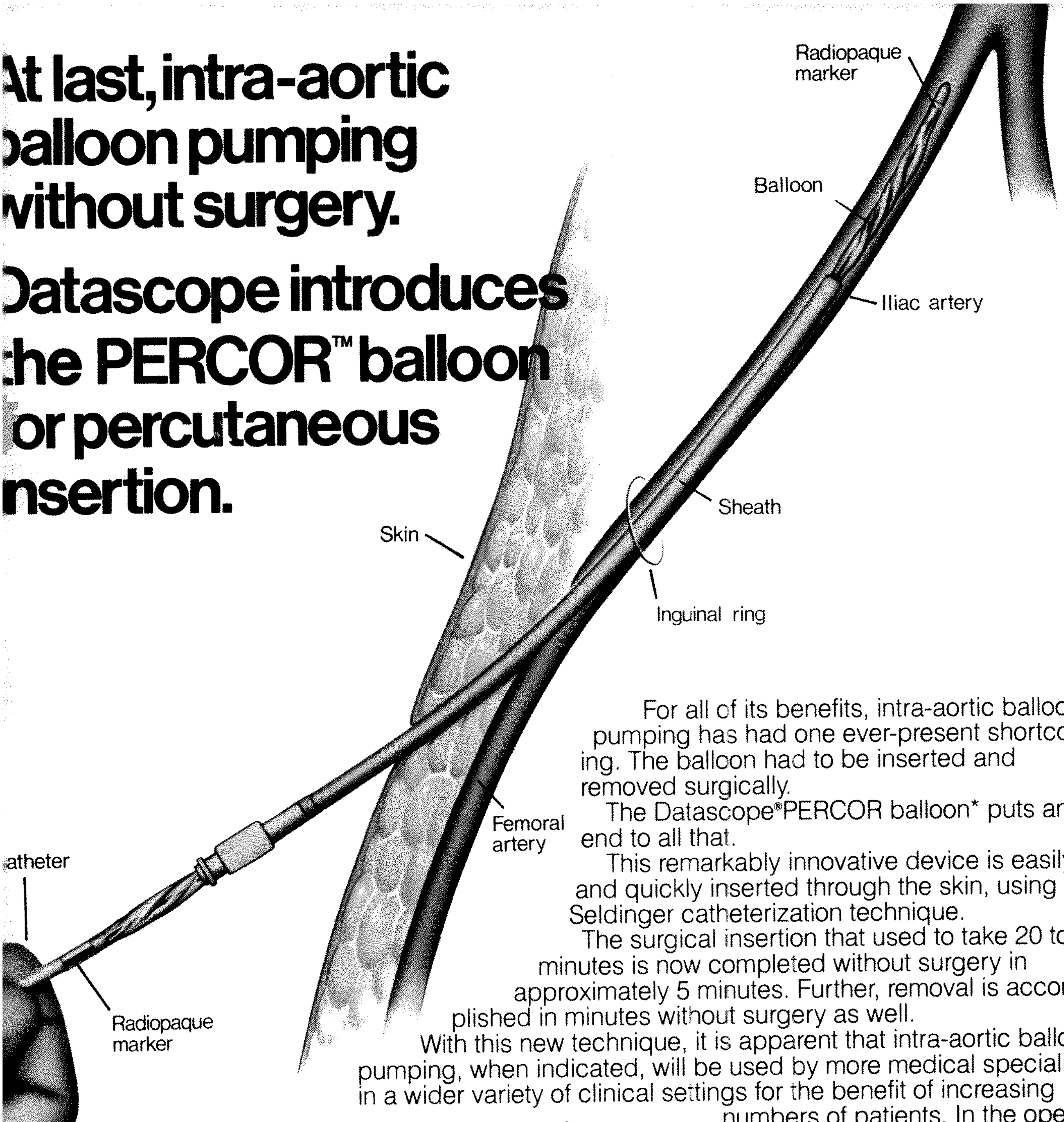

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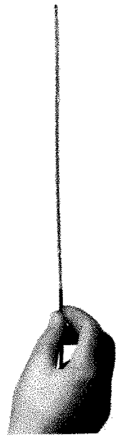

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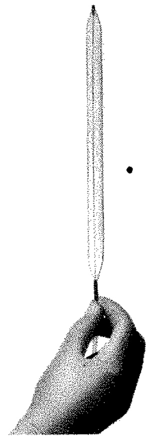

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Clinical reference: *Preliminary Clinical Experience With Percutaneous Intra-Aortic Balloon Pumping (IABP)*, V. A. Subramanian, Jonathan Goldstein, Thomas A. Sos, John C. McCabe, Eddie Hoover & William A. Gay, Jr., New York Hospital, New York, NY. Abstract published in CIRCULATION, Part II, Vol. 60, No. 4, October 1979, PP. II-103. *U.S. and foreign patents pending.

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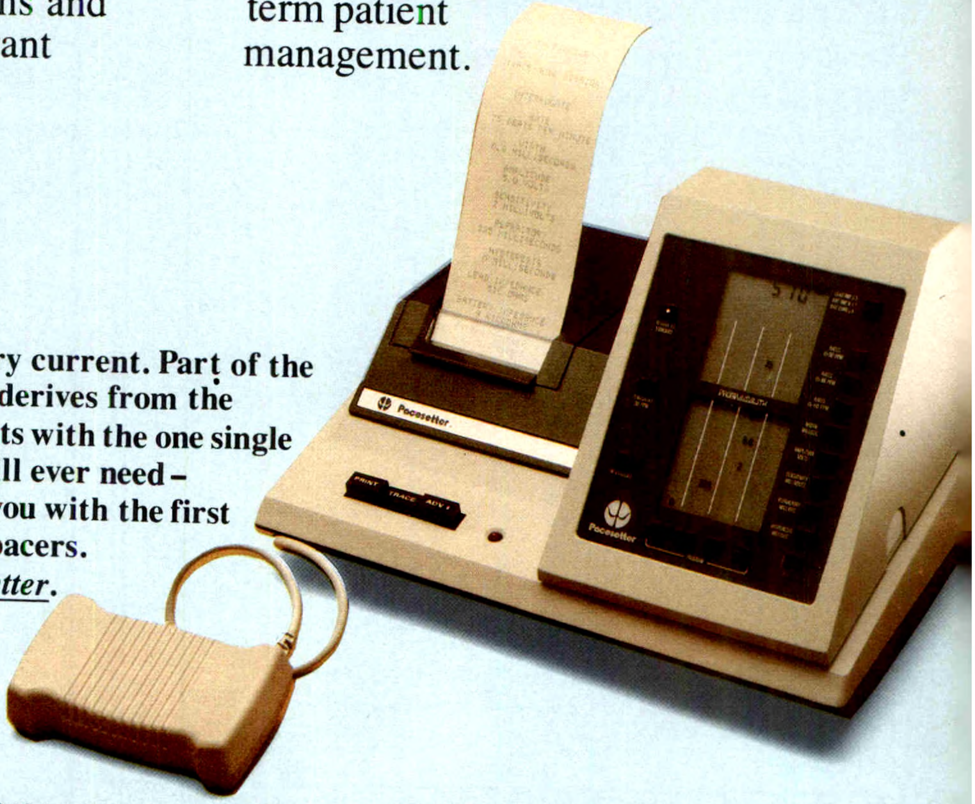

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EDITORIAL

Hypothermic Cardioplegia

William A. Gay, Jr., M.D.

The deliberate lowering of temperature for the purpose of reducing metabolic rate probably began in the early 1600s with the clinical studies conducted by Sanctorius [1]. The practical application of hypothermic techniques to cardiac surgery occurred in the late 1940s when Bigelow and associates [2] reported that dogs kept at 20° to 25°C tolerated total circulatory interruption for a period of fifteen minutes. In 1953, Lewis and Taufic [3] reported the use of hypothermia and inflow occlusion for closure of an atrial septal defect. In the middle and late 1950s, profound (less than 10°C) cardiac hypothermia and total-body hypothermia were used in selected cardiac and neurosurgical procedures [4–6]. The clinical use of topical cardiac hypothermia as an effective mechanism of protecting the heart during aortic cross-clamping was conclusively demonstrated by the Stanford group in 1973 [7]. More even myocardial cooling was obtainable by selective cardiac perfusion and intracavitary lavage with coolant in a subsequent study [8].

Over the past several years, the subject of intraoperative myocardial protection has received considerable attention in the surgical literature and at scientific meetings. After hundreds of reports on this topic, most investigators can agree on two basic concepts—that cold is effective in affording the heart some degree of protection during periods of interrupted coronary flow and that some form of cardioplegia enhances the protective effect of hypothermia. At this point, however, agreement ends and controversy begins. Just what *is* the ideal milieu, both in terms of hypothermia (*how cold, how fast, how induced*) and cardioplegia (*how much of what, mixed in what,* and *given how often*)? If these questions were put to a hundred different cardiac surgeons, there would likely be a hundred different answers, each enthusiastically given. Furthermore, while it remains true that even the smallest tidbit of scientific information has merit, the recent inundation of our senses with so many of these tiny morsels may have resulted in premature intellectual satiety. This point was brought out clearly in a recent communication by McGoon [9].

The study by Swanson and associates (this issue, p 519) asks, and satisfactorily answers, one question: "Does 4°C hypothermia offer better myocardial protection than 15°C"? Although documentation of the level of myocardial temperatures attained is not mentioned, it does appear that, in the conditions of this study, canine hearts protected using the 4°C technique functioned better after two hours of circulatory interruption than those protected with the 15°C technique. An additive effect of cardioplegia to the hypothermia was demonstrated also, as was a superiority of blood cardioplegia when compared with two crystalloid solutions. One aim of this study apparently was to refute a prior claim by Tyers and his associates [10] that 4°C hypothermia resulted in myocardial damage, presumably due to membrane injury. If this is so, why then did Swanson and co-workers elect to use a different experimental animal (the dog instead of the rat) and a different experimental protocol?

With each group of investigators extolling the advantages of *their* solution administered *their* way and evaluated with *their* protocol in *their* laboratory, there is little wonder that no agreement can be reached among investigators as to which technique and which solution is best. I find myself in total agreement with Kirklin [11] who recently said: "If somebody told me, and it were really true and he could prove it, that he had a method of myocardial protection which resulted in zero deaths, zero myocardial infarction and zero functional impairment I wouldn't be interested in anything else about it." I don't think, however, that any of the investigators in this area have arrived at that point. In an effort to provide a degree of standardization in techniques and terminology, some form of cooperative effort among investigators in this field seems warranted at this time.

From the Cornell University Medical Center and New York Hospital, 525 E 68th St, New York, NY 10021.

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It would seem prudent to approach this through the agencies most listened to by the investigators, that is, the funding agencies (such as the National Institutes of Health [NIH] and the American Heart Association) and the reporting agencies (the editorial boards of journals and the program committees of scientific societies). While the amount of research activity associated with myocardial protective techniques currently in progress is laudable, the uncoordinated approach now in use is almost certain to result in a degree of confusion among the readers of journals and the audiences at national meetings. Since this area of investigation is likely to continue for a number of years, I issue a plea to the Study Sections of NIH and the Research Councils of the American Heart Association as well as other agencies concerned with research funding to appoint a panel for the purpose of developing a reasonably standardized protocol for investigating myocardial protective techniques. Similarly, if the editorial boards of the major journals in cardiac surgery and cardiac physiology were to require that these studies be conducted in a reasonably standard way and conform to standard reporting techniques including statistical analyses, the readers would stand to benefit greatly. Similar instructions could go out from the program committees of our national organizations that only studies conforming to agreed upon standards would be acceptable.

The scientific community, especially in the medical sciences, has traditionally been a free-wheeling and independent group of individualists. This has definite advantages in so far as the development and nurturing of new ideas is concerned. Once an idea has been developed to a certain point (a point that has, I think, been reached in the area of myocardial protection), a coordinated effort (such as that used by the National Aeronautics and Space Administration to get men on the moon) seems much more effective.

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Improved Myocardial Preservation at 4°C

David K. Swanson, Ph.D., John H. Dufek, P.A.,
and Donald R. Kahn, M.D.

ABSTRACT **We tested the ability of various cardiac preservation techniques to preserve left ventricular function of isolated canine hearts using preservation temperatures of 4° or 15°C. The four techniques tested were: (1) topical hypothermia, and hypothermic arrest induced by (2) perfusion of 1 liter of a modified Collins solution, (3) perfusion of 1 liter of a modified extracellular solution (DKS), or (4) perfusion of 500 ml of blood cardioplegia. Following the cold ischemia period, the hearts were reperfused with blood in the working heart preparation and tested for their ability to recover left ventricular function.**

Hearts preserved 2 hours at 15°C using hypothermia, modified Collins solution, or DKS solution achieved an average of 60, 73, and 95%, respectively, of baseline function. Hearts preserved 3 hours at 4°C using topical hypothermia attained 70% of baseline function, while hearts stored 5 hours at 4°C using modified Collins solution or DKS solution recovered 83 and 92%, respectively, of baseline function. Hearts preserved at 4°C functioned at levels equal to or greater than that of hearts stored at 15°C, even though the hearts preserved at 4°C were stored for longer periods than those preserved at 15°C. Hearts preserved with blood cardioplegia for 2 hours at either 4° or 15°C achieved functions statistically the same as baseline levels during the reperfusion period.

These data show no advantage for preservation temperatures of 15°C compared with 4°C. Our data provide a firm experimental basis for the clinical use of myocardial preservation temperatures of 4°C, especially when combined with cardioplegia.

From the Division of Thoracic and Cardiovascular Surgery, Clinical Science Center, University of Wisconsin, Madison, WI.

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Address reprint requests to Dr. Swanson, Division of Thoracic and Cardiovascular Surgery, University Hospitals and Clinics, 600 Highland Ave, Madison, WI 53792.

It has been suggested recently by several investigators [2, 6 16, 20] that cardiac preservation at temperatures below 10°C is inferior to that obtained at 10° to 15°C. Yet many cardiac surgeons [1, 3, 8, 9, 14, 19] continue to report excellent myocardial protection using profound topical hypothermia (less than 10°C) with or without cardioplegia Because of this controversy, many surgeons are uncertain as to what temperature is best for myocardial preservation. We have tested the ability of various cardiac preservation techniques to preserve left ventricular function in the canine heart using temperatures of either 4°C or 15°C. Our data provide a firm experimental basis for the clinical use of 4°C topical myocardial hypothermia, especially when combined with cardioplegia.

Material and Methods

Four techniques were evaluated for their ability to preserve left ventricular function of dog hearts following cold ischemia; each technique was tested at both 4° and 15°C. The techniques included (1) topical hypothermia, and hypothermic arrest induced by (2) 1 liter of a modified extracellular solution (DKS), (3) perfusion of 1 liter of modified Collins solution, or (4) perfusion of 500 ml of blood cardioplegia. The formulations of the fluids used to arrest the hearts are shown in Table 1. Control hearts were not exposed to ischemia. In each experimental group, 5 hearts were removed from dogs and placed on a working heart preparation with less than one minute of ischemia. The hearts were tested for baseline ventricular function and then were exposed to cold ischemia. Following the ischemia period, the hearts were reperfused with blood in the working heart preparation and tested for their ability to recover left ventricular function.

Mongrel dogs weighing 17 to 25 kg were anesthetized with intravenous injections of sodium thiamylal (25 to 30 mg per kilogram of body weight), followed by subcuticular in-

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Table 1. Composition of Preservation Solutions[a]

Modified Extracellular Solution		Modified Collins Solution		Blood Cardioplegia	
Component	Concentration	Component	Concentration	Component	Quantity
0.9% Sodium chloride	80 mEq/L	Dibasic potassium phosphate	57.5 mEq/L	Beef lung heparin	3,000 U
Potassium chloride	40 mEq/L	Hydrochloric acid	10 mEq/L	Blood	300 ml
Sodium bicarbonate	25 mEq/L	Magnesium sulfate	8.1 mEq/L	Lactated Ringer's	180 ml
Monobasic potassium phosphate	1.2 mEq/L	Sodium bicarbonate	10 mEq/L	Potassium chloride	18 mEq
Mannitol	100 mEq/L	Glucose	139 mEq/L	CPD additive solution	10 ml
		Mannitol	100 mEq/L	THAM (tromethamine)	4 mEq base

[a]Components listed in the order in which they are added.
CPD = citrate-phosphate-dextrose.

jections of atropine (800 μg). Each dog was intubated and placed on a volume-controlled ventilator with a tidal volume of 30 ml per kilogram. In preparation for dissection with electrocautery, each dog was paralyzed with 20 mg of intravenously administered succinylcholine. The dog was opened with a midline incision, the heart was prepared for isolation, and the dog was heparinized with a dose of beef lung heparin, 3 mg per kilogram. Details of the surgical procedures are described elsewhere [17].

Flow cannulas were inserted into the left atrium and aorta, and connected to the heart perfusion circuit. Then the heart was isolated, with the heart perfusion circuit supporting the heart. After stabilizing the heart in situ, perfusion was stopped, the heart was transferred from the chest to the preservation chamber, and perfusion was reinstituted. Total warm ischemia time was always less than a minute. After five minutes of stabilization, the baseline left ventricular function was measured. Five minutes following completion of the baseline function test, the heart was subjected to a preservation technique.

After preservation, the hearts again were perfused in the isolated heart preparation. Aortic pressure, initially 50 mm Hg, was increased to 60 mm Hg after five minutes of perfusion. Left ventricular decompression was maintained by manually withdrawing blood from the left atrial flow cannula. If spontaneous defibrillation did not occur within ten minutes of reperfusion, the heart was defibrillated with a direct-current shock of 10 watt-seconds. Additional shocks were applied as required to maintain a synchronized beat.

Following successful defibrillation, aortic pressure was increased to 70 mm Hg. After thirty minutes of perfusion, the heart was tested for its ability to pump blood by slowly beginning left atrial flow. Left atrial pressure was kept at 5 mm Hg or lower for the first hour of perfusion, except for short times of elevated left atrial pressure to determine left ventricular function. Left ventricular function was also measured at 1, 1.5, and 2.5 hours following preservation. Coronary blood flow and coronary sinus blood gases were measured at each work level during the left ventricle function test.

Figure 1 illustrates the perfusion circuit used for the isolated working dog heart preparation. Left ventricular cardiac output, aortic pressure, and blood gases are controlled independently. Coronary sinus blood flow is measured with an in-line electromagnetic flowmeter. The technique was described in detail elsewhere [17].

Measurements

We used graphs of stroke volume versus left atrial pressure as the basis for our evaluations of

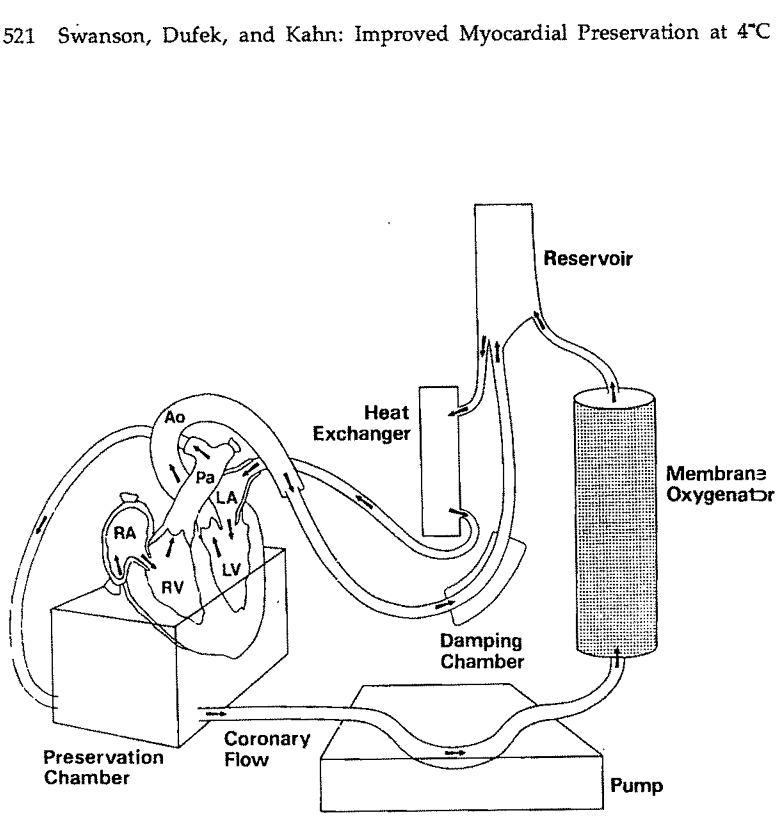

Fig 1. Isolated working dog heart preparation. The perfusion circuit permits the heart to be perfused retrograde through the aorta in the nonworking heart. In addition, cardiac output and aortic pressure can be independently varied to assess left ventricular strength and function in the working heart. (Ao = *aorta;* Pa = *pulmonary artery;* LA = *left atrium;* RA = *right atrium;* RV = *right ventricle;* LV = *left ventricle.)*

function (Fig 2). Baseline left atrial flows were 1,000 ml per minute and mean aortic pressures were 90 mm Hg. To test function, left atrial flows were increased in increments of 500 to 1,000 ml per minute at time intervals of one to two minutes while mean arterial pressure was held constant. Left atrial flow rate was increased until left atrial pressure reached 15 mm Hg, at which time the flow rate was returned to baseline levels. Stroke volumes attained at mean left atrial pressures of 15 mm Hg were used to compare ventricular function between groups.

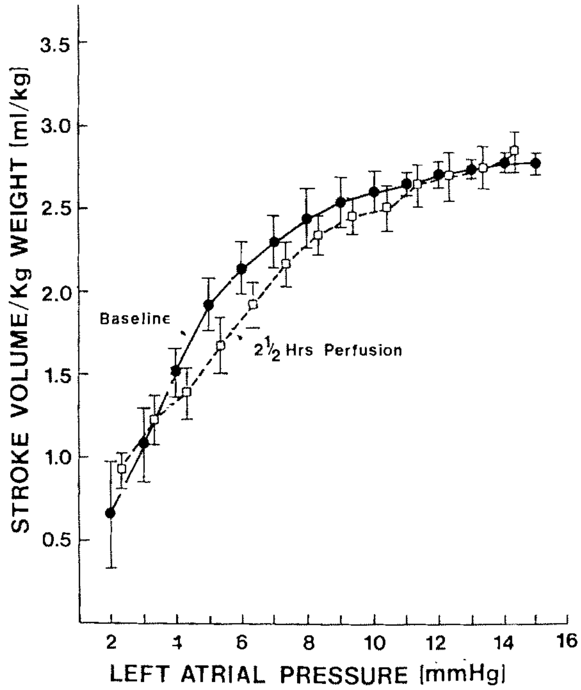

Fig 2. Stroke volume versus left atrial pressure of control hearts at a mean aortic pressure of 90 mm Hg. Each point on the function curves represents the mean value of 6 control hearts; the bars indicate standard error of the mean. Each curve was determined at the indicated time following isolation.

Hemodynamic and blood gas measurements were taken following at least one minute of stabilization at each flow rate. The following were measured at each flow rate: heart rate, aortic pressure, left atrial pressure, coronary blood flow, and coronary blood gases. Stroke work, coronary sinus blood oxygen content, hemoglobin saturation, and cardiac oxygen consumption were computed from measured variables. Stroke work was computed by the formula $SW = SV \times (\overline{Ao} - \overline{LAP})$ where SV is stroke volume, $\overline{Ao}$ is mean aortic pressure, and $\overline{LAP}$ is mean left atrial pressure. Hemoglobin saturation and blood oxygen content were determined by the formulas developed by Rossing and Cain [15]. Oxygen consumption was determined by multiplying the difference of arterial and coronary sinus oxygen contents by coronary blood flow.

Following the evaluation period, the heart was removed from the perfusion system and examined for gross signs of myocardial damage. A full-width section was taken from the posterior papillary muscle for evaluation of tissue water and ionic content. The section was divided into three parts of approximately equal widths containing the subendocardial, midmyocardial, and subepicardial muscle. The samples were weighed, dried to constant weight (more than 24 hours at 80°C), and then reweighed. Dried samples were digested for more than 8 hours with concentrated nitric acid. The sodium and potassium concentration of the tissue was determined by measuring supernatant ion concentrations with a Beckman Klina flame photometer.

Results obtained from each group are expressed as mean ± the standard error of the mean. We used the unpaired Student *t* test to determine the significance of differences in function between groups. Statistical significance of changes caused by a particular preservation technique was determined by using the paired Student *t* test, with data obtained following preservation compared with baseline data.

Preservation Techniques

CONTROL. Control hearts were maintained on the isolated working dog heart preparation for 3.5 hours. Function tests were done thirty minutes following isolation and at hourly intervals thereafter.

TOPICAL COLD. Following baseline function tests, hearts were submerged in 1 liter of 0.9% sodium chloride at 4° or 15°C. Hearts were gently massaged to replace warm blood in the right ventricle with cold saline solution to increase the cooling rate of the ventricular septum. Left atrial and aortic flow cannulas were capped to ensure that no air flowed down the coronary arteries upon reperfusion. The cold saline solution was changed twice at two-minute intervals to maximize cooling rates. Following initial cooling, the heart was placed in the cold saline bath for the remainder of the preservation period.

COLD STORAGE WITH PRESERVATION SOLUTIONS. Hearts were flushed with 1 liter of cold (15° or 4°C) preservation solution at low perfusion pressures (30 to 40 mm Hg). Following the initial flush, the hearts were submerged in another liter of the cold solution for the remainder of the preservation period.

COLD STORAGE WITH BLOOD CARDIOPLEGIA. Hearts were flushed with 500 ml of cold blood cardioplegia at low perfusion pressures (30 to 40 mm Hg). Following the initial flush, the hearts were submerged in 1 liter of 5% glucose and 0.2% sodium chloride at either 15°C or 4°C for the remainder of the preservation period

Results

Control Hearts

Control hearts were able to achieve stroke volumes of 2.5 ± 0.1 ml per kilogram of body weight (mean ± SEM) at a left atrial pressure of 15 mm Hg and a mean aortic pressure of 90 mm Hg (see Fig 2). Left ventricular function was constant for the 3.5 hours of isolation. The only change noted in the control hearts was an increase in coronary blood flow. For the first 2.5 hours of perfusion, the heart extracted 45 ± 5% of available oxygen from the blood, but by 3.5 hours of reperfusion, the hearts preserved at 4°C increased significantly ($p < 0.02$) from 1.2 ± 0.2 to 1.8 ± 0.15 ml/min/gm and oxygen extraction had decreased to 30 ± 4%. Coronary blood flow increased markedly with increases in work loads throughout the control period. At the end of 3.5 hours of isolation, the hearts had normal water content and normal tissue sodium and potassium concentrations (Table 2).

Topical Hypothermia

Three hours of preservation using topical hypothermia at 4°C caused myocardial damage, but the damage was less than that found in hearts preserved 2 hours at 15°C. Following 1.5 hours of reperfusion, the hearts preserved at 4°C recovered 70 ± 10% of baseline left ventricular function, while hearts preserved at 15°C recovered 60 ± 5% of baseline function. The functions were statistically the same at this time point. However, at 2.5 hours of reperfusion, hearts preserved at 4°C had significantly higher

Table 2. Tissue Data Obtained from Hearts Preserved at Temperatures of 4° or 15°C with Differing Cardioplegic Agents[a]

Preservation Conditions			Tissue Data		
Cardioplegic Method	Temperature (°C)	Time (hr)	Water/Dry Weight	Sodium/ Dry Weight (mEq/kg)	Potassium/ Dry Weight (mEq/kg)
Control	...	...	3.50 ± 0.04	260 ± 5	390 ± 4
Topical hypothermia	4	3	4.15 ± 0.07	340 ± 16	360 ± 11
Topical hypothermia	15	2	4.30 ± 0.09	...	...
Collins	4	5	3.85 ± 0.10	...	...
Collins	15	2	3.90 ± 0.12	...	...
DKS	4	5	3.55 ± 0.09	278 ± 8	386 ± 11
DKS	15	2	3.60 ± 0.07	297 ± 11	393 ± 9
Blood cardioplegia	4	2	3.57 ± 0.10	265 ± 11	365 ± 8
Blood cardioplegia	15	2	3.48 ± 0.07	275 ± 16	362 ± 9

[a] A discussion of the data is contained in the Results section.

Table 3. Function of Canine Hearts Preserved with Differing Cardioplegic Agents Stored at Temperatures of 4° or 15°C[a]

Preservation Conditions			Left Ventricular Function		
Cardioplegic Method	Temperature (°C)	Time (hr)	Baseline Function[b]	Function at 1.5 Hours of Reperfusion (%)	Function at 2.5 Hours of Reperfusion (%)
Topical hypothermia	4	3	2.24 ± 0.20	70 ± 10	72 ± 8[c]
Topical hypothermia	15	2	2.35 ± 0.22	60 ± 5	37 ± 5[c]
Collins	4	5	2.01 ± 0.15	83 ± 7	83 ± 6
Collins	15	2	2.41 ± 0.18	73 ± 9	84 ± 7
DKS	4	5	2.46 ± 0.10	90 ± 5	94 ± 8
DKS	15	2	2.33 ± 0.24	91 ± 11	95 ± 7
Blood cardioplegia	4	2	2.49 ± 0.16	97 ± 7	102 ± 6
Blood cardioplegia	15	2	2.46 ± 0.21	98 ± 7	97 ± 5

[a] Data are expressed as mean ± standard error of the mean.

[b] Baseline functions are expressed as stroke volume per kilogram of dog weight measured at a mean left atrial pressure of 15 mm Hg.

[c] $p < 0.02$.

function ($p < 0.02$) than those preserved at 15°C. The hearts preserved at 4°C functioned at 72 ± 8% of baseline levels, while hearts preserved at 15°C functioned at only 37 ± 5% of normal. Four of 5 hearts preserved at 15°C had decreasing function for perfusion times greater than 1.5 hours, while hearts preserved at 4°C maintained constant function (Table 3).

Modified Collins Solution

Hearts preserved with the modified Collins solution for 5 hours at 4°C recovered the same function as hearts stored in Collins for only 2 hours at 15°C (see Table 3). At 1.5 hours of reperfusion, the hearts had attained 83 ± 7% and 73 ± 9% of baseline function, respectively. Ventricular function was also statistically the

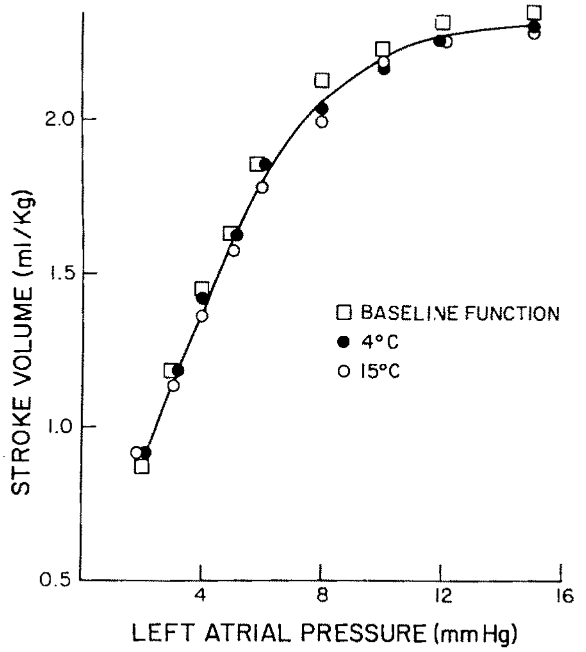

Fig 3. Stroke volume versus mean left atrial pressure at a mean arterial pressure of 90 mm Hg of hearts preserved with blood cardioplegia. Left ventricular function of hearts preserved 2 hours at either 4° or 15°C were statistically the same as baseline. Each point on the function curves represents the mean value found in one of the experimental groups.

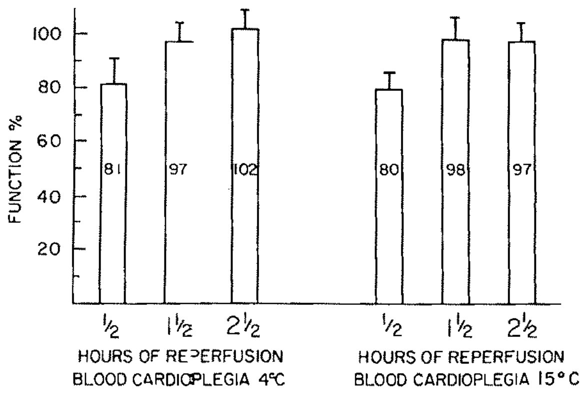

Fig 4. Functional recovery of hearts preserved with blood cardioplegia for 2 hours at temperature of 4° or 15°C. The rates of recovery were statistically the same.

same in the two groups following 2.5 hours of reperfusion, with hearts preserved at 4° and 15°C functioning at 83 ± 6% and 84 ± 7% of normal, respectively. The preserved hearts required an hour to recover 60% function; the rapid phase of recovery was complete in 1.5 hours. Hearts in both groups gained an average of 10% water weight.

DKS Solution

Hearts preserved with the DKS solution for 5 hours at 4°C attained statistically the same function as hearts preserved by the DKS solution for only 2 hours at 15°C. At 1.5 hours of reperfusion, the preserved hearts had attained 90 ± 5% and 91 ± 11% of baseline function, respectively. Ventricular function was also statistically the same in the two groups following 2.5 hours of reperfusion, with hearts preserved at 4° and 15°C functioning at 94 ± 8% and 95 ± 7% of baseline levels, respectively.

Hearts preserved at 15°C gained 3 ± 2% (NS, no statistical significance) in water weight, lost 1 ± 2% (NS) of tissue potassium, but gained 14 ± 4% ($p < 0.02$) in tissue sodium. Hearts preserved at 4°C gained 0 ± 3% (NS) in water weight, lost 1 ± 3% (NS) of tissue potassium, and gained 7 ± 3% (NS) in tissue sodium. There was no statistical difference between groups in any of these tissue measurements. The left ventricles appeared grossly normal in both groups.

Blood Cardioplegia

Hearts preserved with blood cardioplegia for 2 hours at 15°C returned to functional levels statistically the same as baseline (Fig 3). The left ventricles had no change in water weight, the tissues gained 6 ± 5% (NS) of baseline sodium and lost 10 ± 3% ($p < 0.05$) of baseline potassium. The left ventricles appeared grossly normal.

Hearts preserved with blood cardioplegia for 2 hours at 4°C also returned to functional levels statistically the same as baseline (see Fig 3). The left ventricular tissue gained 2 ± 2% in weight (NS), gained no sodium, but lost 10 ± 3% of baseline potassium ($p < 0.05$). Cut surfaces of all left ventricles had a normal appearance.

Hearts preserved at 4°C recovered at statistically the same rate as those preserved at 15°C and reached the same functional level (Fig 4). In addition, there was no significant difference between these groups in tissue water content, tissue sodium, tissue potassium, or coronary flow.

Data Summary

Hearts stored in a modified Collins solution or in the DKS solution at 4°C for 5 hours functioned at statistically the same level as hearts stored in these solutions at 15°C for only 2 hours. Hearts preserved using topical hypothermia alone functioned better following storage at 4°C for 3 hours than at 15°C for 2 hours. Our data show that for these preservation techniques, hearts can be preserved longer at 4°C than at 15°C and still recover the same post-preservation function.

Hearts preserved with blood cardioplegia for 2 hours at either 4° or 15°C achieved functions statistically the same as baseline levels. These data also showed no advantage for preservation temperatures at 15°C compared with 4°C, and no evidence was found that temperatures of 4°C damage the heart.

Comment

Several investigators [2, 6, 16, 20] recently suggested that optimal temperatures for heart preservation are between 10° and 15°C, and that preservation temperatures of 4°C damage the heart [20]. However, we found that preservation at 4°C was superior to that obtained at 15°C when using topical hypothermia, Collins solution, or DKS solution to protect the canine heart. Hearts preserved at 4°C achieved an average function equal to or greater than that of hearts stored at 15°C, even though hearts preserved at 4°C were stored for longer periods than those preserved at 15°C (see Table 3). Furthermore, hearts preserved with blood cardioplegia for 2 hours at either 4° or 15°C achieved functions statistically the same as baseline levels during the reperfusion period.

The data of Tyers and co-workers [20] showed that rat hearts perfused with 10 ml of 10° or 15°C Krebs-Henseleit buffer prior to 1 hour of ischemic arrest, functioned better following a 1-hour ischemia period than hearts perfused with 4°C Krebs-Henseleit buffer. These researchers suggested that their rat hearts were permanently damaged by exposure to temperatures of 4°C. They further hypothesized that cell membrane structure was permanently damaged due to solidification of membrane lipids and that the membrane ATPase system was permanently damaged due to exposure to temperatures of 4°C. In our experiments, we found no evidence of myocardial damage attributable to 4°C temperature alone. Numerous other investigators [4, 6, 13, 18] also successfully employed 4°C preservation of the heart, with little permanent damage to those hearts.

In 1979, Jacobsen and colleagues [7] showed that rapid cooling of kidneys from 37° to 4°C damages them. Kidneys may be especially sensitive to "thermal shock" since they can be cooled at high rates using a cold perfusate (their vascular resistance is low).

In our experiments, we cooled dog hearts at rates about three times slower than the cooling rates found to be damaging to kidneys. On the other hand, Tyers and associates [20] cooled their rat hearts using perfusion flow rates of about 60 ml per gram of dry weight of tissue, which was about twenty times greater than the flow rate we used. Therefore, it is possible that their rat hearts were damaged by rapid cooling rates, since those same cooling rates are known to damage kidneys.

Perfusion of an unmodified extracellular solution such as Krebs-Henseleit solution at 4°C causes tissue edema, even when cooling rates are controlled. Membrane-bound ATPase is inhibited at temperatures below 15°C [11], thereby inactivating the Na^+-K^+ pump. The resultant influx of Na^+ ions into the cell causes intracellular edema [10], reducing the ability of the heart to recover from an ischemia period. As previous investigators [18] have shown, the addition of an oncotic agent to the cold perfusate prevents that tissue water accumulation. Our data confirm that heart temperatures can be safely reduced to 4°C by using well-designed perfusates and low cooling rates.

Behrendt and Jochim [2] stated that the use of a 4°C perfusate decreases diastolic compliance. A 4°C perfusate can cause edema and stiffness in the left ventricle by the mechanism already described. However, our data show that myocardial temperature can be reduced to 4°C during an ischemia period and still not have significant loss of diastolic compliance. Although we did not measure compliance directly, we were able to infer that the diastolic compliance of hearts preserved with blood cardioplegia did not change significantly. Graphs of left atrial pressure versus stroke volume were virtually identical before and after 4°C preservation (see Fig 3), strongly suggesting that compliance was constant.

Follette and associates [5] suggested that blood sludging could occur if blood cardioplegia was administered at 4°C. We found no evidence of tissue damage due to sludging of our blood cardioplegic fluid at 4°C. The hematocrit of our formulation was 20%—evidently low enough to retard aggregation of red cells.

Because of heat transfer from the chest, temperature within the in vivo heart is not uniform. The use of multidose cold blood cardioplegia appears to be a solution to this problem since blood cardioplegia completely protected heart tissue for 2 hours at temperatures of both 4° and 15°C. A potential advantage of the use of 4°C cardioplegia rather than warmer perfusates is that poorly perfused areas of the heart are better cooled by adjacent well-perfused areas.

Our data show that canine hearts can be cooled to 4°C without damaging myocardial function. Furthermore, preservation times could be extended when the myocardium was cooled to 4° rather than 15°C. Our results provide a firm experimental basis for the clinical use of myocardial preservation temperatures of 4°C, especially when combined with cardioplegia.

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Improved Oxygen Delivery to the Myocardium during Hypothermia by Perfusion with 2,3 DPG–Enriched Red Blood Cells

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ABSTRACT **The oxygen affinity of red cells increases stepwise with temperature reductions below 37°C. In vitro studies demonstrated that biochemically modified red cells with increased 2,3 diphosphoglycerate (2,3 DPG) (150% and 250% of normal) exhibited significantly less oxygen affinity at 24°C than did unmodified cells. At 15°C, significant attenuation of affinity was observed with 250%, but not 150%, of normal 2,3 DPG cells.**

Measurements made of isolated fibrillating dog hearts during perfusion at 24°C alternately with unmodified (80% of normal 2,3 DPG) and modified (300% of normal 2,3 DPG) red cells demonstrated significantly greater oxygen consumption, higher coronary sinus partial pressures of oxygen and carbon dioxide, higher in vitro P_{50} values, and lower arterial and coronary sinus lactate levels during perfusion with modified as compared with unmodified cells. This evidence, indicating improved oxygen delivery to hypothermic dog hearts by red cells with 300% of normal 2,3 DPG activity, suggests that high 2,3 DPG cells might protect myocardial tissue in patients undergoing hypothermic cardiac operation.

Hypothermia and potassium-containing cardioplegic solutions with or without blood have been used to protect the myocardium during open-heart operations [1, 8–23, 26–33, 36, 37, 42–45]. Hypothermia protects the heart during cardiac operation by reducing myocardial oxygen demand. On the other hand, hypothermia also reduces the availability of oxygen to the myocardium by increasing the oxygen affinity of the red blood cells. This affinity for oxygen is increased further by increases in blood pH and reductions in partial pressure of carbon dioxide (Pco_2) during hypothermia [35]. What has been regarded in general as a reduction in oxygen consumption during hypothermia may actually be a reduction in oxygen availability.

Studies have shown that increasing the levels of 2,3 diphosphoglycerate (2,3 DPG) and adenosine triphosphate (ATP), especially 2,3 DPG, attenuates the increased affinity of red blood cells for oxygen at low temperatures [2, 24]. The initial experiments in the present study were designed to evaluate the relation between 2,3 DPG level and red cell oxygen affinity at various temperatures. In vitro studies were carried out on human red blood cells with 2,3 DPG levels approximately 70%, 150%, and 250% of normal at temperatures of 37°C, 24°C, 15°C, and 10°C. In addition, isolated hypothermic dog hearts at 24°C were perfused with red blood cells with 80% of normal (nonrejuvenated) and 300% of normal (rejuvenated) 2,3 DPG levels, in the course of which arterial blood and coronary sinus blood were serially tested for partial pressure of oxygen (Po_2), Pco_2, pH, lactate concentration, oxygen content, and oxygen consumption.

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The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or Naval Service at large.

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The animals used in this study were handled in accordance with the provisions of Public Law 89-44 as amended by Public Law 91-579, the "Animal Welfare Act of 1970," and the principles outlined in the "Guide for the Care and Use of Laboratory Animals," United States Department of Health, Education, and Welfare Publication No. (NIH) 72-23.

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Materials and Methods

In Vitro Studies of Oxygen Affinity

The oxygen affinity of human red cells with 70%, 150%, and 250% of normal 2,3 DPG was measured at different temperatures. Three units of O-positive citrate-phosphate-dextrose (CPD) anticoagulated blood were obtained from healthy human volunteers. The red blood cells were concentrated to a hematocrit of 75 vol per 100 ml and stored at 4°C for 6 to 8 days. The 3 units were then pooled and immediately separated into three equal portions. One of the three portions was incubated at 37°C for 1 hour with 50 ml of PIGPA Solution A, a rejuvenating solution containing 50 mmole/L of pyruvate, 50 mmole/L of inosine, 100 mmole/L of glucose, 50 mmole/L of disodium phosphate, 5 mmole/L of adenine, and 9 gm/L of sodium chloride, pH 7.2, producing an increase in 2,3 DPG to approximately 150% of normal. The second portion, similarly treated with 50 ml of PIGPA Solution B, containing 100 mmole/L of pyruvate, 100 mmole/L of inosine, 100 mmole/L of glucose, 200 mmole/L of disodium phosphate, 5 mmole/L of adenine, and 5 gm/L of sodium chloride, pH 7.2, had a 2,3 DPG level approximately 250% of normal. The third portion, serving as control, biochemically unmodified, had a 2,3 DPG level approximately 70% of normal.

Each of the 3 units of red cell concentrate was glycerolized to a final concentration of 40% w/v and then divided into three further 130 ml aliquots, making a total of nine aliquots. Each aliquot was frozen and stored at −80°C in a mechanical refrigerator, storage periods ranging from a few days to 6 months.

On three separate occasions during storage, one aliquot from each unit was removed from the refrigerator for evaluation. Each aliquot was thawed and was washed sequentially with 12% sodium chloride, 1.6% sodium chloride, and a solution containing 0.9% sodium chloride, 0.2% glucose, and 25 mEq/L of disodium phosphate. A modification of the washing procedure for the IBM Blood Processor 2991-1, as previously described [38], was used.

The in vitro oxygen tension at which 50% of the hemoglobin was saturated was determined in triplicate at 37°C, 24°C, 15°C, and 10°C by modifications of the spectrophotometric technique of Bellingham and Huehns [3]. This value is referred to as the in vitro P_{50}. The temperatures were controlled both in the water bathing the tonometer for the washed red blood cells and in the cuvette holder of the spectrophotometer. The Po_2 in the tonometer at the time of measurement was calculated from the standard gas law. The 2,3 DPG and ATP levels were determined as previously described [38].

Perfusion of Isolated Hypothermic Dog Hearts with Human Red Cells Containing 80% and 300% of Normal 2,3 DPG

Human red blood cells were used to perfuse the dog hearts in this study. This is an acceptable procedure as long as the dog plasma is first removed to avoid heterophile erythroagglutination.

Approximately 450 ml of blood was collected from each healthy O-positive volunteer into 63 ml of CPD anticoagulant in a triple plastic-bag collection system,* then centrifuged in an RC-3 refrigerated centrifuge† at 3,700 revolutions per minute (3,550 × *g*) for 10 minutes. The red blood cells were concentrated to a hematocrit value of 75 vol per 100 ml and stored for 3 to 5 days at 4°C. The stored red cell concentrates were divided into two equal portions. One portion was untreated and served as control. The other half was biochemically modified with PIGPA Solution B [39]. Modification of red cell concentrates was similar to that of the in vitro studies except that the pretreatment storage period was 3 to 5 days instead of 6 to 8 days. Both the modified and control preparations were frozen with 40% w/v glycerol and stored at −80°C for periods of at least a year. Prior to the perfusion studies, the red cells were thawed, washed, and suspended in an albumin-crystalloid solution. Thawing took about 10 minutes at 37°C. and sodium chloride solutions were used for washing the red cells in the Haemonetics blood processor with the original disposable polycarbonate bowl [38]. The washed unit was concentrated by centrifugation, and all the supernatant was removed. The

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†Dupont Instruments, Newtown, CT.

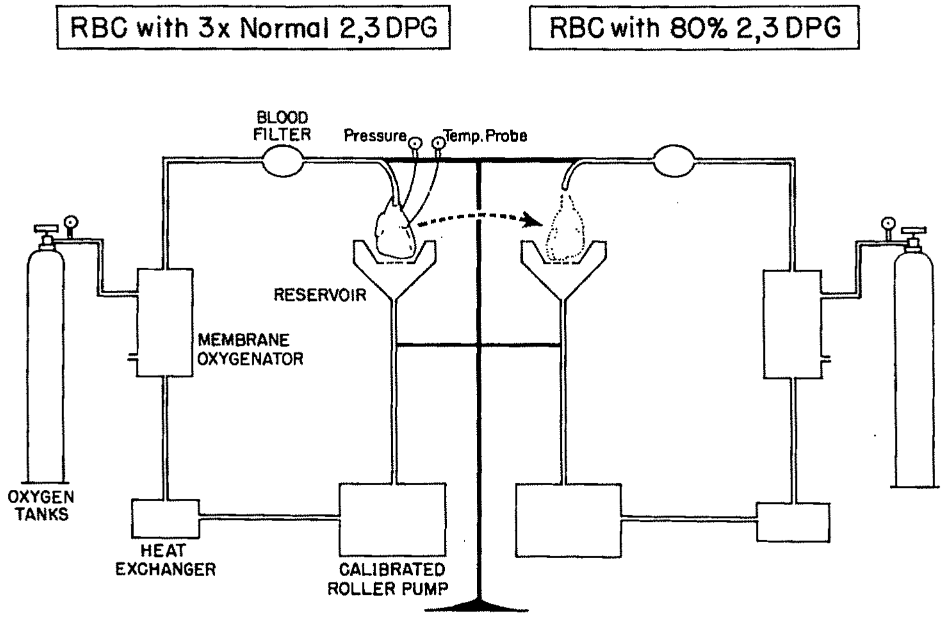

Fig 1. Diagram of the system used to perfuse the isolated dog heart with rejuvenated and nonrejuvenated human red blood cells (RBC).

red blood cell concentrate was diluted with the albumin-crystalloid solution used to flush the dog blood from the coronary circulation, and the hematocrit of the red blood cell–albumin–crystalloid solution was adjusted to 30 vol per 100 ml.

Each mongrel dog was sedated with 30 mg of phencyclidine hydrochloride (Sernylan) and 130 mg of pentobarbital. Following endotracheal intubation for mechanical ventilation, the heart was exposed through a median sternotomy. The brachiocephalic artery was cannulated. The heart was isolated by dividing the superior vena cava, inferior vena cava, azygos vein, pulmonary artery, and the thoracic aorta distal to the brachiocephalic trunk. In order to prevent agglutination of the human red blood cells by canine plasma, the dog blood was washed from the coronary circulation by perfusion of the aortic root with an isotonic solution of 50 gm/L of albumin, 2.1 gm/L of sodium bicarbonate, 5 gm/L of sodium chloride, 300 mg/L of potassium chloride, 1 gm/L of glucose, 11.2 mg/L of monobasic potassium phosphate, 48 mg/L of dibasic sodium phosphate, 100 mg/L of calcium chloride, maintained at 5°C at 100 ml per minute for 15 minutes. The heart was excised and placed in an extracorporeal circuit (Fig 1) consisting of a Buckner reservoir, a calibrated roller pump, a Travenol disposable heat exchanger, and a Travenol membrane oxygenator (model 5M-0936). Three gas tanks were connected to the circuit and, through adjustable flow valves, delivered 100% oxygen, 5% carbon dioxide–20% oxygen–75% nitrogen, and 3% carbon dioxide–20% oxygen–77% nitrogen. The circuit was completed by Tygon tubing. The left and right ventricles were vented by stab wounds, and a needle thermistor was inserted into the interventricular septum to monitor myocardial temperature. Aortic root perfusion pressure was displayed continuously.

After the canine blood was washed out, the mechanical pump was primed with 2 units of blood, and each isolated dog heart was perfused at 100 ml per minute for 1 hour with 2 units of nonrejuvenated or rejuvenated red blood cells. The system was then flushed for an hour through a new, separate circuit with 700 ml of the other type of cell suspension (rejuvenated or nonrejuvenated). This was followed by a third hour of perfusion with the second blood prime. In 2 of the fibrillating hearts, the nonrejuvenated red blood cells (80% of normal 2,3 DPG) were used during the first hour, followed by rejuvenated cells (300% of normal 2,3 DPG). In the other 2 fibrillating hearts, rejuvenated red blood cells were perfused first, followed by nonrejuvenated blood. The Po_2, Pco_2, and pH of the perfusate were controlled at physiological levels by the introduction of appropriate gas mixtures and addition of sodium bicarbonate as required. The temperature was maintained at 24°C during the entire experiment.

Samples were obtained every 15 minutes during the first and third hour of the experiment, but not during the washout period, from the aortic root and from the coronary sinus blood as it exited from the right ventricular vent. Supernatant hemoglobin, extracellular potassium ion, and red blood cell 2,3 DPG and ATP were measured as previously described [38]. Arterial and coronary sinus Po_2, Pco_2, and pH were measured at 37°C in the IL-313 Blood Gas Analyzer* and the values were corrected to 24°C using the Severinghaus nomogram [35]. Total hemoglobin was measured by the cyanmethemoglobin procedure in a Coleman spectrophotometer. The percent oxyhemoglobin and percent carboxyhemoglobin were measured in the IL-182 Co-Oximeter.* The oxygen content in arterial and coronary sinus blood was measured in the Lex-O_2-CON fuel cell† and calculated from the total hemoglobin, the percent oxygen saturation, and the dissolved oxygen [41]. The dissolved oxygen was calculated from the Po_2 at 24°C and the solubility constant of 0.0042 at 24°C [34].

Upon completion of perfusion, the isolated heart was weighed, and oxygen consumption was calculated as ml/min/100 gm of myocardial tissue from the arteriovenous difference in oxygen content multiplied by coronary blood flow, which was controlled by the calibrated roller pump. Blood lactate was measured in the arterial blood and coronary sinus blood [25]. The Po_2, measured at 37°C and corrected to 24°C, and the percent saturation of available hemoglobin were used to calculate the in vitro P_{50} value by the Hill equation, assuming an n value of the oxyhemoglobin dissociation curve of 2.7 [39, 40]. Lactate production by the red blood cells with 80% of normal 2,3 DPG and with 300% of normal 2,3 DPG was measured after 3 hours of incubation at 37°C in an albumin-crystalloid solution.

Results

Baseline measurements made on washed fresh heparinized red blood cells indicated the P_{50} value of the oxyhemoglobin dissociation curve to be 27.0 ± 1.0 mm Hg (mean ± standard deviation at pH 7.2, $Pco_2 = 0$, and temperature 37°C); carboxyhemoglobin level, 1 to 2%; red blood cell ATP level, 4.5 ± 1.0 μmole per gram of hemoglobin; and red blood cell 2,3 DPG level, 13.5 ± 1.5 μmole per gram of hemoglobin.

In the in vitro study, red blood cells with 150% of normal 2,3 DPG and 125% of normal ATP and red blood cells with 250% of normal 2,3 DPG and 175% of normal ATP had significantly lower oxygen affinity at 24°C and 37°C than did red blood cells with 70% of normal 2,3 DPG and 90% of normal ATP (Figs 2, 3). At 15°C, red blood cells with 250% of normal 2,3 DPG had significantly lower oxygen affinity than did red blood cells with 70% of normal 2,3 DPG or 150% of normal 2,3 DPG. At 10°C, oxygen affinity was not significantly different among the three groups.

Each of 4 isolated fibrillating dog hearts was perfused with red blood cells with 80% of normal 2,3 DPG (nonrejuvenated) and red blood cells with 300% of normal 2,3 DPG (rejuvenated) (Table 1). After 30 minutes of perfusion, the nonrejuvenated red blood cells had 2,3 DPG levels of 80% of normal and the rejuvenated red blood cells had about 300% of normal 2,3 DPG levels. In all 4 isolated hearts, Po_2 and Pco_2 were decreased and pH was increased in the arterial and coronary sinus blood when the measurements made at 37°C were corrected to 24°C, the temperature of the isolated heart. Data from the four samplings were combined to calculate mean values for analysis: measurements of arterial Po_2, Pco_2, and pH and of coronary sinus pH were not significantly different whether nonrejuvenated or rejuvenated red blood cells were perfused (Table 2); measurements of coronary sinus Po_2 and Pco_2, however, were significantly higher (by about 5 mm Hg) after perfusion with rejuvenated red blood cells.

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*Instrumentation Laboratories, Lexington, MA.
†Lexington Instruments, Waltham, MA.

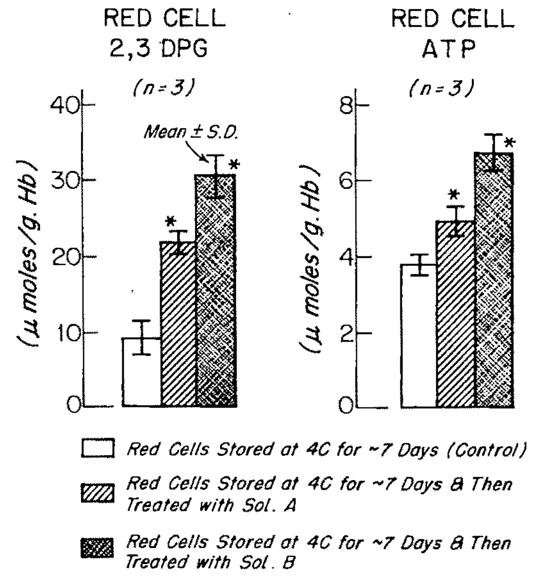

Fig 2. Three units of red blood cells were stored at 4°C for about 7 days and then pooled. The 3-unit pool was divided into three equal units: 1 unit was not rejuvenated (70% normal 2,3 DPG); 1 unit was rejuvenated with PIGPA Solution A (150% normal 2,3 DPG); and the third unit was rejuvenated with PIGPA Solution B (250% normal 2,3 DPG). Each unit was glycerolized to a final concentration of 40% w/v glycerol and then divided into three 130-ml aliquots. Each of the nine aliquots was frozen separately and stored at −80°C. Their red blood cell 2,3 DPG and adenosine triphosphate (ATP) levels are shown. (= $p < 0.05$ [control vs Sol. A or Sol. B].)*

Oxygen consumption was higher after perfusion with rejuvenated red blood cells (see Table 2). Mean values from four samplings indicated that the in vitro P_{50} was significantly higher, arteriovenous oxygen content differences significantly greater, and oxygen consumption significantly higher after perfusion with rejuvenated red blood cells (see Table 2).

At each of four sampling periods, arterial and coronary sinus blood lactate levels were higher after perfusion with nonrejuvenated red blood cells, and when the data from the four sampling periods were combined, the increases were significant (see Table 2). Lactate levels were higher in coronary sinus blood than in arterial blood samples after perfusion with red blood cells containing 80% of normal 2,3 DPG levels. During perfusion with red blood cells containing 300% of normal 2,3 DPG levels, the lactate levels were higher in the arterial blood than in the coronary sinus blood (see Table 2). After incubation of the red blood cells in an albumin-electrolyte solution at 37°C for 3 hours, lactate production was not significantly different between the nonrejuvenated and rejuvenated red blood cells, suggesting that it was the dog's heart that was responsible for the production or utilization of lactate and not the donor red blood cells.

Hemoglobin concentrations in arterial and coronary sinus blood were significantly higher after perfusion with rejuvenated red blood cells because recovery of the red blood cells after the freeze-thaw-wash process was higher in these

Fig 3. The P_{50} values of washed, previously frozen red blood cells with 70% of normal, 150% of normal, and 250% of normal 2,3 DPG at 10°C, 15°C, 24°C, and 37°C are shown. (= $p < 0.05$ [control vs Sol. A or Sol. B].)*

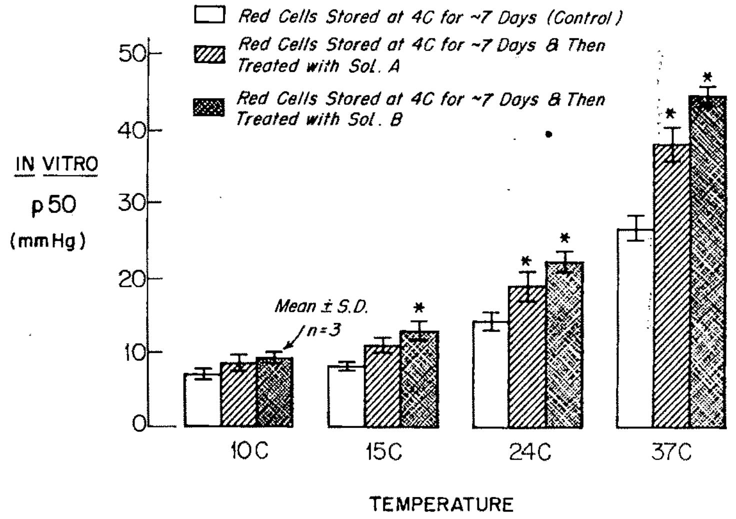

Table 1. 2,3 DPG Levels 30 Minutes after Initiation of Perfusion

Variable	Experiment 1			Experiment 2			Experiment 3			Experiment 4		
Perfusion hour	1	2	3	1	2	3	1	2	3	1	2	3
Perfusate	NR	WO	REJ	REJ	WO	NR	NR	WO	REJ	REJ	WO	NR
2,3 DPG (mm/gm Hb)	10.1	...	38.2	38.0	...	11.8	10.2	...	38.1	40.8	...	12.0

NR = nonrejuvenated red blood cells with 80% of normal 2,3 DPG; REJ = rejuvenated red blood cells with 300% of normal 2,3 DPG; WO = washout between different perfusates.

Table 2. Paired t *Test Combining Four Time Periods for the Four Experiments (n = 16)*

Measurements	300% of Normal 2,3 DPG RBC (Rej)	80% of Normal 2,3 DPG RBC (NR)	*p* Value
O_2 consumption (ml/min/100 gm heart tissue)	0.96 ± 0.16	0.79 ± 0.2	<0.05
AV O_2 difference (vol/100 ml)	3.48 ± 0.60	2.87 ± 0.87	<0.02
Lactate, arterial (μmole/ml blood)	3.51 ± 1.58	4.85 ± 1.34	<0.03
Lactate, coronary sinus (μmole/ml blood)	3.40 ± 1.62	5.44 ± 1.46	<0.01
Hemoglobin, arterial (gm/dl)	9.96 ± 0.54	9.18 ± 0.55	<0.001
Hemoglobin, coronary sinus (gm/dl)	9.92 ± 0.56	9.21 ± 0.52	<0.001
Po_2, arterial, 24°C (mm Hg)	96.4 ± 29.4	80.9 ± 54.0	NS
Pco_2, arterial, 24°C (mm Hg)	25.5 ± 6.26	22.8 ± 3.53	NS
pH, arterial, 24°C	7.59 ± 0.09	7.59 ± 0.05	NS
Po_2, coronary sinus, 24°C (mm Hg)	22.94 ± 2.32	17.87 ± 3.64	<0.001
Pco_2, coronary sinus, 24°C (mm Hg)	22.75 ± 2.18	18.07 ± 3.41	<0.001
pH, coronary sinus, 24°C	7.54 ± 0.16	7.56 ± 0.15	NS
In vitro P_{50}, 24°C (mm Hg)	14.08 ± 0.94	9.89 ± 1.56	<0.001

RBC = red blood cells; Rej = rejuvenated; NR = nonrejuvenated; AV = arteriovenous; Po_2 = partial pressure of oxygen; Pco_2 = partial pressure of carbon dioxide.

units (see Table 2): the freeze-thaw-wash recovery was 90% (mean, 89.1 ± 4.5, n = 10) for rejuvenated red blood cells and 85% (mean, 84.7 ± 5.6, n = 10) for nonrejuvenated red blood cells.

Comment

Although the relative merits of cold and potassium during ischemic arrest are debated, it is almost universally recognized that the combination of these two modalities in the form of hypothermic cardioplegia provides the best protection for the myocardium. The most commonly employed method of producing cold cardioplegia is through the use of a cold asanguineous crystalloid solution containing potassium. Recently, however, a blood vehicle has been suggested in order to meet the residual oxygen requirements of the relaxed cold heart. According to Buckberg [9], oxygenated blood has several advantages: (1) it prevents the depletion of high-energy phosphate stores during the short period of electromechanical activity in the fibrillating heart before asystole is achieved; (2) it replenishes ATP stores during the period of ischemic arrest; (3) it obviates the need to add substrate for prolonged anaerobic metabolism; and (4) it provides the oncotic component, thereby eliminating the need for the addition of plasma, mannitol, or dextran to the cardioplegic solution.

The major advantage of a blood vehicle is, however, essentially predicated on the delivery of oxygen to the myocardium. Although hypothermia reduces myocardial oxygen requirements, the cold temperature also decreases oxygen availability to the tissues by raising the oxygen–hemoglobin affinity state. This bond is further enhanced by an increase of blood pH and a reduction of Pco_2 during hypothermia. It is probable that the observed decrease in oxygen utilization during hypothermia may be in part due to reduced oxygen availability secondary to the enhanced affinity state. It is also likely that if the hemoglobin-oxygen bond were weakened, the myocardium would consume more substrate. Thus, the attenuation of the hemoglobin–oxygen affinity state may facilitate higher oxygen utilization and thereby improve myocardial protection during ischemic arrest of the heart.

The increase of red cell 2,3 DPG levels attenuates oxygen affinity and increases oxygen availability to the tissues. The present experiment was designed to study the strength of the bond at various temperatures and to observe the influence of various levels of blood 2,3 DPG on this relationship. Additionally, we also investigated the impact of elevated 2,3 DPG levels on myocardial metabolism in an isolated heart preparation.

The in vitro studies reaffirmed the fact that with decreasing temperatures, the hemoglobin-oxygen bond is strengthened and consequently oxygen availability to the tissues decreases. At 24°C, oxygen availability can be increased by the use of blood containing 150% and 250% of normal 2,3 DPG while at 15°C, only blood with the higher level of 2,3 DPG is effective. At 10°C, however, raising the level of 2,3 DPG in the blood even to the higher levels employed in this study has no beneficial influence on oxygen availability to tissues.

Perfusion of isolated dog hearts with human blood appears to be an acceptable experimental model as long as the dog blood is adequately washed out and heterophile antibody agglutination thereby prevented. Our isolated canine heart experiments demonstrate that, at low temperatures, an increase in 2,3 DPG blood levels facilitates oxygen release to the tissues and the myocardium takes advantage of the improved oxygen availability. Transmyocardial oxygen extraction and oxygen consumption increase. Additional evidence of aerobic metabolism is provided by data suggesting a reduction in arterial and coronary sinus lactate levels and transmyocardial lactate extraction instead of production. It is evident from the present observations that raising the level of 2,3 DPG in cold blood improves oxygen availability to the tissues and that the resultant aerobic metabolism enhances myocardial protection.

Oxygen in physical solution in plasma increases with lowering of temperature, an increase that may offset in small part the stronger hemoglobin-oxygen bond and may improve to some degree the quality of myocardial protection. Hyperbaric oxygen was once, but is no longer, used during surgical repair of cyanotic congenital heart defects to increase the amount of oxygen dissolved in blood and increase oxygen availability [4–7].

The perfusion studies reported in this paper indicate that elevated 2,3 DPG levels exert additive protective influence by further facilitating aerobic metabolism as evidenced by increased oxygen consumption. Our previous studies in man have indicated that the use of high 2,3 DPG blood for transfusion during open-heart operations improved myocardial performance as documented by a favorable shift in left ventricular volume loading function curves [13]. The present experiment in the isolated heart provides more direct evidence for the beneficial influence of red cells with high 2,3 DPG levels in coronary perfusates. Based on this information, we think that increasing 2,3 DPG levels in the blood used as a vehicle for delivery of cardioplegia enhances myocardial preservation, and therefore we have instituted a clinical study using a blood cardioplegic agent with a high 2,3 DPG content.

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Interstitial Fluid Pressure Changes during Cardiopulmonary Bypass

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Walter P. Dembitsky, M.D., Alan R. Hargens, Ph.D.,
and Richard M. Peters, M.D.

ABSTRACT **The effects of cardiopulmonary bypass using hemodilution on interstitial fluid pressure were measured using the Scholander wick technique. In 10 mongrel dogs, interstitial fluid pressure was measured in subcutaneous tissue, skeletal muscle, stomach, and left ventricle before and during 2 hours of cardiopulmonary bypass. Changes in interstitial fluid pressure were correlated with plasma colloidal osmotic pressure and duration of bypass. In subcutaneous tissue and skeletal muscle, interstitial fluid pressure increased during bypass; it did not change in the stomach. End-diastolic interstitial fluid pressure in the left ventricle increased significantly.**

These increases in pressure were presumably due to an increase in interstitial water. The rise in interstitial fluid pressure acts to partially neutralize the fall in plasma colloidal osmotic pressure.

Low cardiac output and heart failure due to myocardial dysfunction is common following cardiopulmonary bypass (CPB). Clinical and experimental studies have demonstrated myocardial necrosis, hemorrhage, and edema [7, 30]. Decreased ventricular compliance and performance have been attributed to myocardial edema incurred during CPB [1, 9, 12, 33, 34]. Several studies showed increases in body extravascular water content and in the heart [6, 40] following hemodilution [6, 10, 11, 25, 26, 38]. Decreased myocardial blood flow due to increased intramyocardial pressures is a cause of subendocardial necrosis [7, 21, 37, 39]. A number of techniques have been used to measure intramural pressures in the normal and edematous heart [13, 22, 23, 33]. Guyton and colleagues [18] pointed out that these methods measure *total tissue pressure* instead of *interstitial fluid pressure,* which is the dynamic component of total tissue pressure directly related to edema formation.

Utilizing the Scholander wick catheter, we have investigated changes in interstitial fluid pressure in the heart and other organs during CPB in dogs. The wick catheter has been used in several animal and human studies to study changes in interstitial fluid pressure. It has been applied in the measurement of subcutaneous tissue pressure, brain tissue pressure [36], and recently in the diagnosis of compartment syndromes in human subjects [31]. We report here the effects of hemodilution on interstitial fluid pressure in several tissues and describe the application of the wick catheter technique to similar measurements in clinical situations.

Methods

The Wick Catheter

Our catheters utilize the principles described by Scholander and colleagues [35], and we have employed the revisions described by Hargens and co-workers [19], with minor changes. The wick was composed of a 3 cm length of braided soluble No. 2 Dexon suture (polyglycolic acid, with a uniform fiber diameter of 20 μ), but recently we have switched to a 30 cm length of 6-0 Prolene monofilament suture tied to the midpoint of the wick and threaded through a 25 cm length of polyethylene tubing (inner diameter, 0.53 mm; outer diameter, 0.965 mm; polyethylene, size 50). The monofilament suture is used to pull the Dexon wick fibers into the proximal end of the polyethylene tubing, and a blunt, 23-gauge Luer-Lok needle is threaded over the end of the monofilament suture and

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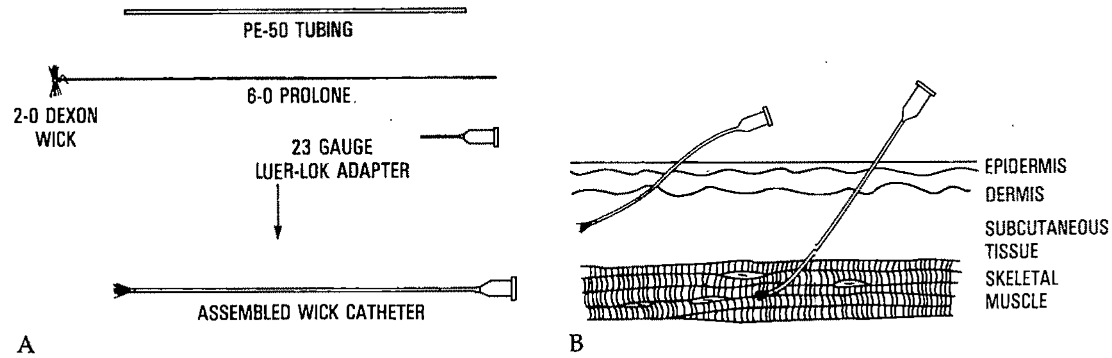

Fig 1. Components of the wick catheter: (A) assembled catheter and (B) position of placement. (PE = *polyethylene.)*

into the distal end of the polyethylene tubing (Fig 1A). The Dexon wick is trimmed to extend 5 to 7 mm from the end of the polyethylene tubing, and the monofilament is cut just inside the blunt needle hub. This provides access to the wick, should it slip out of the catheter.

Catheters are gas sterilized for patient use. The catheter assembly must be filled with heparinized saline solution (5 IU per milliliter) prior to use. The catheter is connected by a three-way stopcock to a Gould-Statham P23Db transducer and a PhysioSentinel stripchart recorder. To insert the wick, an Angiocath 16-gauge intravenous catheter placement unit is introduced into the tissue at the desired depth and the steel trocar withdrawn 1 cm so that the point lies within the soft Teflon sheath. The sheath is advanced through the tissue for 3 to 5 mm and the steel trocar removed. The wick catheter is introduced into the tissue through the remaining Teflon sheath. When the catheter is at the desired site, the Teflon sheath is slowly withdrawn from the tissue, and the wick catheter is secured in place with 5-0 silk suture or tape (Fig 1B). Pressure can be recorded immediately.

Experimental Technique

Ten mongrel dogs weighing 20 to 30 kg were anesthetized with intravenously administered sodium pentobarbital (25 mg per kilogram of body weight) and arterial, central venous, and pulmonary capillary wedge pressures were monitored. Baseline measurements were obtained for the following: hematocrit, arterial and mixed venous partial pressure of oxygen (Po_2), partial pressure of carbon dioxide (Pco_2) and pH, plasma colloidal osmotic pressure,* serum electrolytes, and protein. Median sternotomy was performed and CPB established through a single venous cannula in the right atrium and a left femoral artery cannula.

Wick catheters were inserted in the subcutaneous tissue and skeletal muscle of the animal's right hind leg, in the muscularis of the fundus of the stomach, and at a depth of 5 mm in the left ventricular mass in the relatively avascular region between the left anterior descending coronary artery and its distal acute diagonal branches. Baseline interstitial fluid pressure measurements were recorded and CPB initiated at a flow rate of 70 to 80 ml/kg/min and a mean arterial pressure of 80 mm Hg. A Med-Science roller pump and a Temptrol pediatric oxygenator with a 1 liter Ringer's lactate prime solution were used. Hypothermia (30°C) was maintained with a heat exchanger. Cardiopulmonary bypass was maintained for 2 hours in each animal. Interstitial fluid pressures were recorded at 15-minute intervals. Plasma colloidal osmotic pressure, hematocrit, serum electrolytes and protein, and arterial and venous Po_2, Pco_2, and pH were recorded at 30-minute intervals. After each experiment, a postmortem examination was performed to confirm the location of the wick catheters.

Results

Figure 2 shows the changes in plasma colloidal oncotic pressure, hematocrit, and total protein

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*Weil Oncometer System 186: Instrument Laboratory, Lexington, MA; UM 10 membrane: Amicon, Lexington, MA.

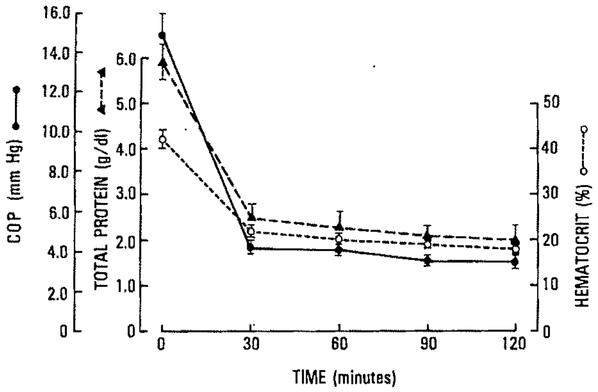

Fig 2. At the start of cardiopulmonary bypass, there is an acute fall in hematocrit, plasma colloidal osmotic pressure (COP), and protein concentration, followed by gradual, continued decline.

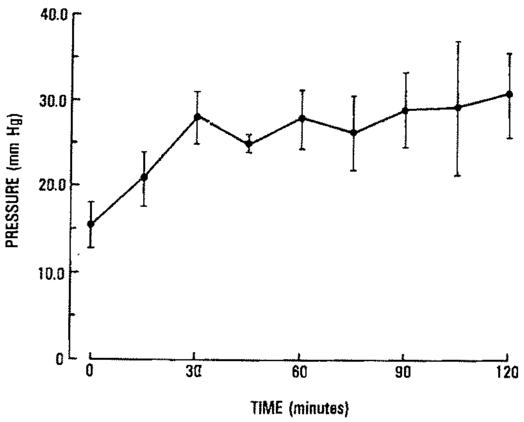

Fig 4. In the myocardium, interstitial fluid pressure during diastole rises acutely with initiation of bypass and continues a slow rise thereafter.

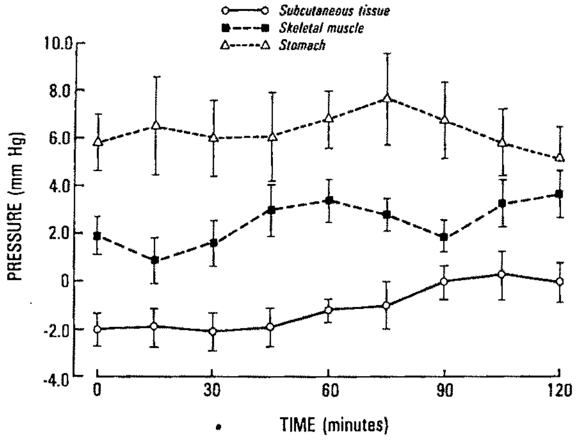

Fig 3. Changes in interstitial fluid pressure of subcutaneous tissue, skeletal muscle, and stomach during bypass. The rise in skeletal muscle pressure is faster than that of subcutaneous tissue, which suggests the subcutaneous interstitial space is loose.

after hemodilution with Ringer's lactate solution during 2 hours of CPB. Each animal received additional Ringer's lactate solution during the experiment to replace losses, to maintain perfusion pressure, or to accomplish both of these. Plasma colloidal osmotic pressure, hematocrit, and serum protein fell significantly ($p < 0.01$) by 30 minutes of CPB. Although additional fluids were added as mentioned, plasma colloidal oncotic pressure, hematocrit, and total protein did not change further after their initial decline.

Figure 3 shows the changes in interstitial fluid pressure during 2 hours of CPB. Control dogs (data not shown) with similar instrumentation but without CPB showed no changes in pressure over a 2-hour observation period.

The baseline interstitial fluid pressure of subcutaneous tissue was subatmospheric. Following an initial decline of 8%, the pressure increased significantly ($p < 0.05$) after CPB. Similar increases in interstitial fluid pressure were seen in subcutaneous sites other than the hind leg (e.g., chest wall, abdomen).

In skeletal muscle, the initial interstitial fluid pressure was above that of the atmosphere. The pressure initially declined by approximately 50%, but by the conclusion of CPB 2 hours later, it had increased significantly ($p < 0.05$) to 91% above baseline values.

Interstitial fluid pressure recorded in the muscularis of the fundus of the stomach was initially positive and did not change significantly ($p > 0.05$) over the 2-hour period of CPB. This pressure was quite responsive to distention of the stomach by air or food, rising twofold to threefold and returning to baseline when the stomach was emptied. Postmortem examination revealed considerable edema in the stomach wall.

Measurement of interstitial fluid pressure in the myocardium during diastole was chosen to eliminate the additional pressure imparted on the interstitium by active tension developed during systole (Fig 4). Figure 5 is a representative tracing from the myocardial wick, demonstrating the phasic nature of the pressures recorded. Interstitial fluid pressure in the

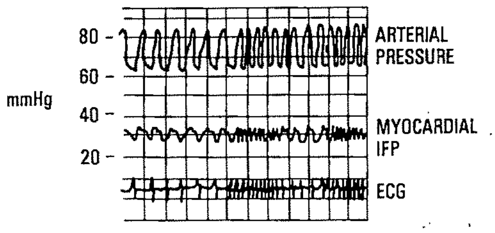

Fig 5. Relationship between arterial pressure and interstitial fluid pressure (IFP). *It is lower than the arterial pressure in the present study.* (ECG = *electrocardiogram.)*

Analysis of Variance Comparing Effects of Time on CPB and Tissue Type on Rate of Increase of Interstitial Fluid Pressure over Baseline

Source	SS	DF	F	p Value[a]
Tissue	18341.1	3	6.49	0.01
Duration of CPB	20754.2	7	3.15	0.05
Error	19772.7	21		

[a] Calculated by F test.

CPB = cardiopulmonary bypass; SS = sum of squares; DF = degrees of freedom; F = F ratio of variances.

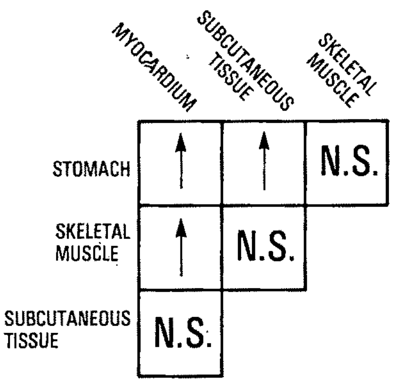

Fig 6. The significance of differences among the four measured interstitial fluid pressure values determined by analysis of variance. The point of the arrow designates that the value at the head of the column or row had a significantly greater ($p < 0.01$) *rate of increase of pressure.* (N.S. = *not statistically significant.)*

myocardium showed a significant ($p < 0.01$) increase over baseline after only 30 minutes of CPB. It continued to increase throughout the 2 hours of CPB and reached a level 100% above the initial value. Interstitial fluid pressures remained near baseline values in control animals not undergoing hemodilution.

A two-way analysis of variance was made to determine how the percent increase in interstitial fluid pressure over the baseline value in each tissue was affected by the duration of CPB (Table). Considering all tissues together, the percent increase over baseline became significant ($p < 0.05$) after 105 minutes of CPB. For myocardium alone, this occurred much sooner (30 minutes). There was also a significant difference ($p < 0.01$) in the rate of increase in interstitial fluid pressure between tissues as expressed by the percent increase in this pressure from baseline over time. Figure 6 diagrammatically shows the relationships among tissues. Interstitial fluid pressure in the myocardium increased at a rate significantly greater than that in the skeletal muscle and stomach, but did not differ statistically from the pressure in subcutaneous tissue. The rate of increase in interstitial fluid pressure in subcutaneous tissue was greater than it was in the stomach, but did not differ significantly from the pressure in skeletal muscle or the myocardium. The rate of increase in interstitial fluid pressure in skeletal muscle was greater than it was in subcutaneous tissue or the stomach, but did not reach statistical significance ($p > 0.05$). The rate of increase of interstitial fluid pressure in skeletal muscle was significantly less than in the myocardium.

Comment

A variety of techniques for measuring interstitial fluid pressure have been proposed. Investigators have used two types of methods for measuring interstitial pressure. One type measures subcutaneous tissue interstitial fluid pressure as positive (above atmospheric) and the other, as negative (subatmospheric). Guyton and colleagues [17, 18] have shown that the first method measures *total tissue pressure,* whereas the second method measures *interstitial fluid pressure.*

The first type of method uses two fundamental techniques: the needle and balloon. The needle technique [8, 29, 41], which measures the minimum pressure required to force a minute drop of saline solution into tissue through a fine needle, gives values for interstitial fluid pressure of subcutaneous tissue ranging from 0 to 8 mm Hg. For the balloon technique, a flaccid balloon is inserted in tissues and minimally distended with fluid to equilibrate the fluid pressure recorded inside the balloon with the tissue pressure exerted on the outside of the balloon wall. Variations of the balloon technique have been employed to record intramyocardial pressures [2, 4, 13, 22, 23, 33]. These methods have given values for intramyocardial pressures during diastole of 0 to 10 mm Hg and during systole close to those for intraventricular pressures. A systolic pressure gradient also has been demonstrated with higher pressures in the region closer to the endocardium.

Several key observations suggest that interstitial fluid pressures of subcutaneous tissue may be negative and not positive. McMaster noted intermittent uptake of fluid into the interstitial space when dye or saline solution was brought into contact with it [27, 28]. Clinicians have long recognized the flaccid nature of the surface of a blister during the resorptive phase or of skin when fluid is injected subcutaneously, as during clysis. These observations led to the second type of methods used to measure interstitial fluid pressure, the Guyton perforated capsule and the Scholander wick catheter.

In 1960, Guyton and co-workers [16] demonstrated subatmospheric interstitial fluid pressure in dogs, utilizing chronically implanted perforated plastic capsules [14]. They described two tissue pressures that make up total tissue pressure [17]. Interstitial fluid pressure is the component of total tissue pressure that is transmitted in the tissues by free fluid and, as such, determines fluid movement in tissues (e.g., edema accumulation). Solid tissue pressure is that component of total tissue pressure that is transmitted by the solid tissue fibers and interstitial gels, and thus determines the physical shapes of tissues. Total tissue pressure is the algebraic sum of interstitial fluid pressure and solid tissue pressure and determines the net pressure exerted on parts such as cell surfaces, blood vessels, and bone [18]. Guyton demonstrated an increase in interstitial fluid pressure in subcutaneous tissue in edematous states and the return of this pressure to a negative value with resolution of the edema. He also described compliance characteristics of the subcutaneous interstitial space by constructing pressure-volume curves [15]. The requirement of chronic implantation for use of the Guyton capsule eliminates its use for clinical studies or in tissue sites too small to accommodate the capsule.

Scholander and colleagues [35] in 1968 described use of the wick catheter for measuring interstitial fluid pressure to circumvent the need for chronic implantation. This has allowed investigation of short-term changes in interstitial fluid pressure in experimental animals and in humans [19, 24, 31, 36]. The wick fibers act to increase the surface area exposed to the interstitial space, maintaining patency of the catheter tip. This in effect allows direct measurement of the pressure. Extensive evaluation of this wick catheter has shown it to be an accurate method for measurement of interstitial fluid pressure, and close agreement has been demonstrated with the fundamental precepts of tissue pressure outlined by Guyton using the perforated capsule [19, 24, 32, 35, 36].

We have shown significant increases in interstitial fluid pressure in subcutaneous tissue, in skeletal muscle, and in the heart in experimental animals undergoing CPB. Interstitial fluid pressure in the muscularis of the fundus of the stomach did not change significantly, although it has been shown that hemodilution causes a marked increase in stomach wall water content [40]. Studies in humans undergoing CPB demonstrated similar increases in interstitial fluid pressure in skeletal muscle and subcutaneous tissue during and for 10 hours after plasma colloidal oncotic pressure and total protein returned to levels measured before CPB. The rise in pressure in all tissues was gradual, suggesting the need for equilibration of Starling forces before new static interstitial fluid pressures are reached. The time required for this equilibration also differed between tissue types.

Variation of time delay between tissues indicates that some tissues, i.e., myocardium and skeletal muscle, possess tighter interstitial spaces than others, i.e., stomach wall and subcutaneous tissue. The physical character of the tissue affects the rate of increase in interstitial fluid pressure and the differences in water content in these tissues during CPB. Differences in permeability and protein reflection coefficients of capillary beds of tissues, as well as differences in tissue compliance, may play important roles in interstitial fluid pressure dynamics.

Guyton pointed out that the relationship between interstitial fluid pressure and volume [15] measures the compliance characteristics of the subcutaneous interstitial space. The compliance is determined by the balance between the elastic characteristics ("compaction compliance") of the cells, blood vessels, and interstitial solid elements that would be compressed by an increase in the interstitial fluid volume, and the elastic characteristics ("expansion compliance") of the fascia, skin, and covering surfaces of the tissue that would tend to oppose expansion of the interstitial fluid volume [18]. Guyton found a nonlinear relationship that explains the change in tissue compliance in edematous states. Under these conditions, large increases in interstitial fluid volume result in small changes in interstitial fluid pressure once a critical point on the pressure-volume curve is surpassed. Guyton's studies were limited to the subcutaneous tissues. Our studies suggest that characteristic compliance curves may exist for each tissue in the body, depending on their inherent structure. Further studies are needed to characterize these pressure-volume relationships and evaluate their impact on tissue blood flow.

Myocardial depression after CPB has been attributed largely to myocardial edema and necrosis. It has been shown in animal and human studies that increased total tissue pressure results in a sharp decline in or cessation of tissue blood flow [3]. This is in keeping with the theoretical importance of total tissue pressure proposed by Guyton. In addition, edema decreases the critical closing pressure of the blood vessels [20, 42], which, in turn, results in diminished blood flow to tissues. Brandi and McGregor [5] showed an increase in interstitial fluid pressure proportional to the amount of fluid infused into an interstitial space. We have demonstrated a 100% increase in myocardial interstitial fluid pressure in experimental animals subjected to hemodilution during CPB, and have shown this to be closely associated with decreased plasma colloidal oncotic pressure and the duration of CPB. This increase presumably is due to increase in interstitial water. Similar elevations of interstitial fluid pressure have been shown in the subcutaneous tissue and skeletal muscle of experimental animals. Studies in patients undergoing open-heart operations utilizing CPB demonstrated pressure changes in skeletal muscle and subcutaneous tissue identical to those seen in animals. Interstitial fluid pressure in the myocardium cannot as yet be measured safely in humans.

This study shows the potential importance of controlling interstitial fluid pressure in patients undergoing hemodilution. Further investigations are needed to study interstitial fluid pressure dynamics with hemodilution when plasma colloidal oncotic pressure is maintained at more physiological levels. Inherent characteristics of tissues, such as interstitial space compliance and capillary permeability, require further description to better explain changes in interstitial fluid pressure seen in edematous states. The Scholander wick catheter is a useful experimental and clinical tool for the study of interstitial fluid pressure dynamics.

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A New Instrument for Surgical Creation of an Atrial Septal Defect

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ABSTRACT **An instrument for surgical creation of an atrial septal defect (ASD) was designed and tested in puppies weighing an average of 4.7 kg. Oxygen saturations were obtained in both atria, the superior vena cava, and the inferior vena cava before and after septectomy. The instrument has a cutting cylinder introduced into the right atrium (RA) through the right atrial appendage with a second part (baseplate) inserted into the left atrium (LA) just posterior to the interatrial groove. In 21 animals (Group 1), a single hole was created in dogs killed 48 hours later. In 9 animals (Group 2), an attempt was made to create two adjoining holes. In 14 animals (Group 3), a single hole was created and the dogs were allowed to triple their body weight before they were killed.**

Group 1 dogs demonstrated a 10% increase in average venae cavae—RA oxygen saturation immediately after septectomy and a 9.4 ± 0.37 mm diameter of the ASD at death; in Group 2, there was a 14% average step-up and a 12.7 ± 0.6 mm diameter of the ASD; and in Group 3, the diameter of the ASD was 11.5 ± 0.4 mm, representing a 50% increase in average area with dog growth compared with that of Group 1. After this experience in the production of ASDs in 44 experimental animals, we find that this instrument seems to be reliable, simple, and safe.

Despite the growing emphasis on intracardiac repair of congenital heart defects in infancy, some surgeons still think an infant with transposition of the great arteries (TGA) should be allowed to reach a critical weight before repair is attempted. In an infant with inadequate mixing, a larger interatrial communication must be created until he is large enough for repair. In many patients, this can be accomplished by a Rashkind balloon septostomy at the time of cardiac catheterization. A significant number, however, will require surgical intervention if this proves inadequate. The Blalock-Hanlon operation has been widely used to increase the right-to-left shunt by creating an atrial septal defect (ASD), but this measure is not without complications [2, 3, 6, 7, 12, 19, 33]. For this reason we devised and tested an instrument intended to create an ASD in a simpler and safer manner.

Materials and Methods

Forty-four beagle puppies with an average weight of 4.7 kg (3.5 to 6.6 kg) were anesthetized with intravenously administered sodium pentobarbital (30 mg per kilogram of body weight), intubated, and ventilated with a Harvard respirator. Central venous and arterial blood pressures were monitored through the right femoral vessels, and the heart was exposed through the right chest in the fourth intercostal space.

The septectomy instrument has two parts (Fig 1). One is a cutting cylinder, the center of which is hollow (inside diameter, 8 mm), with a sharp edge to facilitate cutting of septal tissue. This cylinder encloses a removable inner cannula 5 mm longer at its distal end. The 5 mm tip is rounded and allows for easier insertion of the entire cylinder into the right atrium (RA) through a pursestring suture. The second part of the instrument is a baseplate against which the cylinder cuts the septum in a cork-bore fashion (Fig 2). The baseplate is supported by a post, which is attached perpendicularly and has a cylindrical tunnel to guide and hold the cutting cylinder in the appropriate position. The baseplate is inserted into the left atrium (LA) through a pursestring suture of 4-0 Prolene on a choker posterior to the interatrial groove. The cutting cylinder is then introduced into the RA through a similar pursestring suture on the lateral right atrial wall, close to the interatrial

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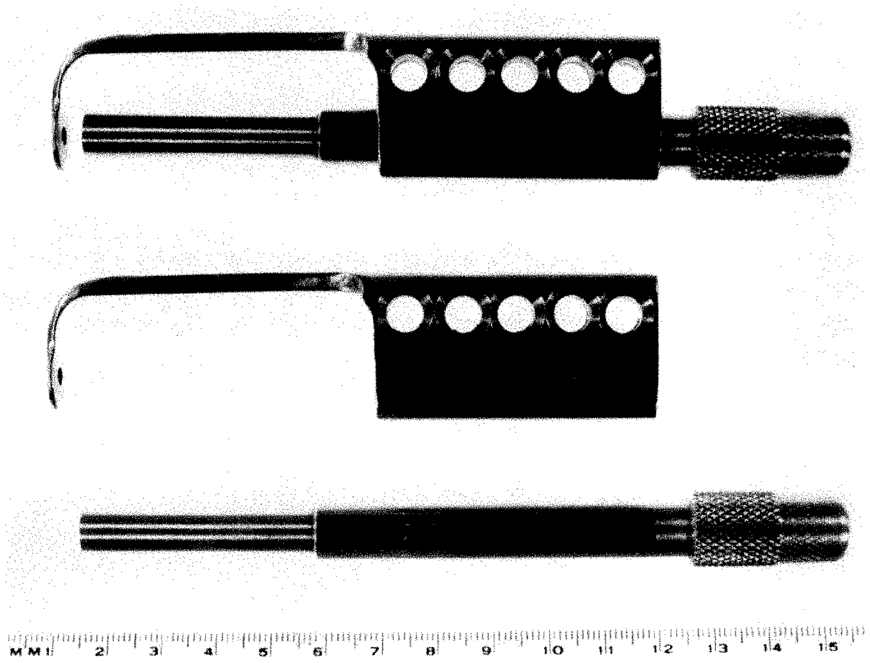


Fig 1. Instrument for creation of atrial septal defect.

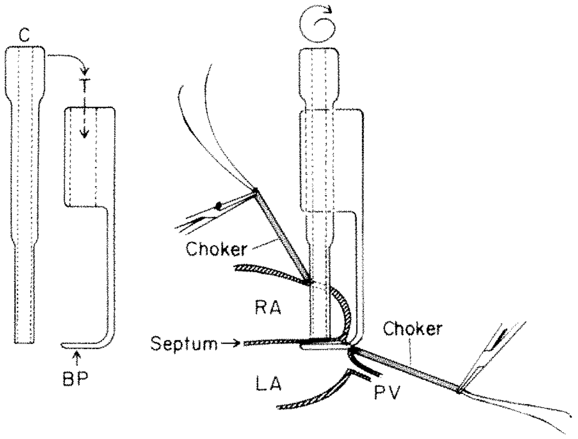


Fig 2. The cutting cylinder (C) *is pressed down upon the baseplate* (BP), *which has a tunnel* (T) *to guide and hold it, and is rotated 360 degrees several times, cutting through the septal tissue. The disc of excised septal tissue is suctioned into the lumen of the cutting cylinder.* (RA = *right atrium;* LA = *left atrium;* PV = *pulmonary vein.)*

groove. The positions of the two parts within each atrium are assured by palpation.

The inner cannula is removed from the cutting cylinder, and the cutting cylinder then is attached to a suction line with an interposed filter. The cutting cylinder (in the RA) is pressed down upon the baseplate (in the LA) and rotated 360 degrees, thereby cutting through the septal tissue. The disc of excised septal tissue is immediately suctioned into the lumen of the cutting cylinder, and trapped in an on-line, transparent filter (Fig 3). The suction line is clamped and the surgeon verifies the presence of septal tissue in the chamber. If septal tissue is not found, the procedure is repeated. Immediately upon confirmation of the presence of septal tissue, the instruments are removed from both atria and the atriotomy wounds closed by the pursestring sutures. Antibiotics were administered for two days to animals in the acute experiment and for one week to those in the chronic experiment.

The 44 animals were divided into three groups. In Group 1 (21 dogs) a single ASD was created, and the animals were killed at 48 hours. In Group 2 (9 dogs), a single ASD was created as in Group 1, followed by an adjoining ASD, made by altering the position of the septome; the dogs were killed at 48 hours. In Group 3 (14 dogs), a single ASD was made and the dogs were allowed to triple their body weight before they were killed in order to allow observation of the effect of growth on ASD size.

In all of the animals, oxygen saturation was obtained intraoperatively from the inferior vena cava, the superior vena cava, the RA,

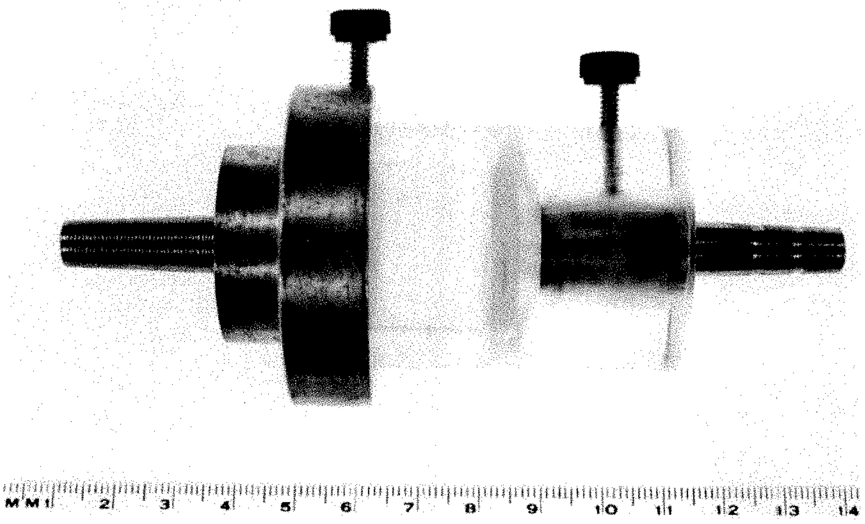


Fig 3. Transparent filter to capture the disc of excised septal tissue.

and the LA prior to and following septectomy. Hemodynamically stable conditions were maintained prior to sampling. Similar measurements were repeated prior to death, at which time the ASD was sized in the undistended state. One standard error of the mean was included in statistical analysis of the data.

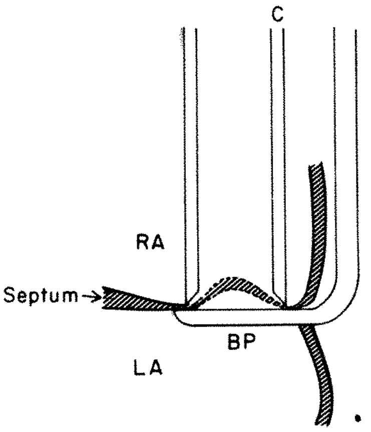


Fig 4. The septum is held over the baseplate (BP) *under the cutting cylinder* (C). *Dotted lines show doming of the septum over the baseplate. This occurs when suction is applied just before pressure is put on the cutting cylinder.* (RA = *right atrium;* LA = *left atrium.)*

Results

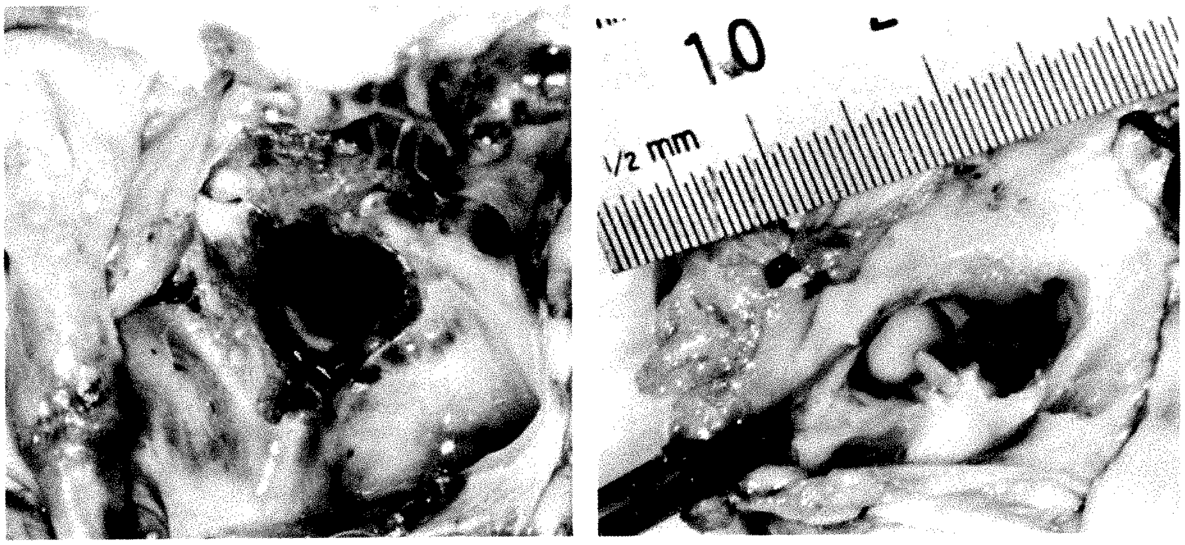
The excised septal tissue was always slightly larger than would be expected from the diameter of the cutting cylinder. This is probably due to a stretching and doming of the septum from the baseplate into the lumen of the cutting cylinder as suction is applied (Figs 4, 5A).

Group 1

Data summarizing the results are listed in the Table. Following septectomy, the RA oxygen saturation increased from 62 ± 2% to 70 ± 3% (8%) intraoperatively, and remained at that level at 48 hours. The average step-up in the venae cavae and RA was 10% after septectomy and 12% at 48 hours. The average ASD diameter was 9.4 ± 0.37 mm. In 1 animal an ASD was not produced; the failure was attributed to bending of the baseplate, which caused faulty apposition of the instrument. No tissue was recovered from the filter. This was corrected, and we encountered no other difficulties in obtaining septal tissue in the remainder of our experiments. Four animals died prior to scheduled death, 3 of obvious pulmonary problems (atelectasis, infection) and 1 of an unknown cause. No puppy died as a result of the septectomy procedure directly.

Group 2

Following septectomy, the RA oxygen saturation increased from 59 ± 4% to 71 ± 1% (12%), and was 73 ± 0.5% (14%) at 48 hours. The average venae cavae–RA step-up was 14% immediately after septectomy and 17% 48 hours later. The average ASD diameter was 12.7 ± 0.6 mm, representing an 83% increase in average area



A

B

Fig 5. Surgically created single (A) and adjoining (B) atrial septal defects.

compared with Group 1 (Fig 5B). One animal died of complete heart block, a death which must be assumed to be directly attributable to the procedure.

Group 3

Twelve of 14 animals underwent successful septectomy and experienced a smooth postoperative course and convalescence. The puppies were followed for an average of 230 days (range, 177 to 317 days), and the body weight increased from 4.3 ± 0.4 kg to 12.8 ± 0.6 kg at the time of death. Following septectomy, the RA oxygen saturation increased from 62 ± 2% to 69 ± 2% (7%) and was 79 ± 3% (17%) at the time of death; the average venae cavae–RA oxygen saturation step-up was 15% at the same time. The average ASD diameter was 11.5 ± 0.4 mm, a 50% increase in average area compared with the average single defect in Group 1. In 1 animal an ASD was not detected, but a fibrotic scar in the appropriate location suggested spontaneous closure of the ASD; septal tissue had been obtained at the operative procedure. Two animals died, 1 of a pneumothorax and 1 of a hemothorax.

Comment

Despite the growing emphasis on intracardiac repair of TGA in infancy, many surgeons still believe that infants should achieve a minimum weight prior to correction [1, 15, 21]. There is greater mortality and morbidity with the Mustard procedure in infants less than 6 months old than in those older than 6 months [10, 28]. One factor supporting earlier repair regardless of size has been the considerably high mortality of

Increase in Oxygen Saturation at the Level of the Right Atrium, and Venae Cavae–Right Atrium Oxygen Saturation Step-up before and after Septectomy

	Increase in Oxygen Saturation[a] (%)		Oxygen Saturation[a] Step-up (%)	
Group	Intraop	Before Death	Intraop	Before Death
1 (N = 21)	8 (62 ± 2 → 70 ± 3)	8[b] (62 ± 2 → 70 ± 2)	10 (60 ± 3 → 70 ± 3)	12[b] (58 ± 2 → 70 ± 2)
2 (N = 9)	12 (59 ± 4 → 71 ± 1)	14[b] (59 ± 4 → 73 ± 0.5)	14 (57 ± 5 → 71 ± 1)	17[b] (56 ± 2 → 73 ± 0.5)
3 (N = 14)	7 (62 ± 2 → 69 ± 2)	17[c] (62 ± 2 → 79 ± 3)	11 (58 ± 3 → 69 ± 2)	15[c] (64 ± 5 → 79 ± 3)

[a] Values in parentheses are mean ± standard error before and after septectomy.
[b] Data at 48 hours postop.
[c] Data at the time of tripling of body weight.

palliative procedures. An operation or instrument that safely creates an ASD may allow more surgeons to delay correction until the infant is considerably larger. In addition, a variety of other congenital defects such as tricuspid atresia occasionally still call for creation of an ASD as the initial operation of choice [18, 22, 24, 30].

The Rashkind balloon septectomy remains the simplest and most attractive method of creating an ASD since it does not require operation and is usually effective [1, 5, 11, 13, 20, 23, 27, 31, 32]. There are, however, occasional failures due to inadequate ASD size and late closure [1, 16, 17]. In general, palliation for TGA involves the creation of an ASD without use of cardiopulmonary bypass [3, 9]. The Blalock-Hanlon procedure has had broadest application since its introduction in 1950, but is not without complications produced by clamping of the right pulmonary vessels [2, 3, 6, 7, 12, 19, 33]. The Edwards atrial shift was used in infants with TGA in the late 1960s [9], but was later abandoned presumably because of poor results and higher risk. Schuster and associates [26] experimentally devised another method of creating an ASD without use of cardiopulmonary bypass, and several instruments have been invented in the hope of simplifying the surgical creation of an ASD. Leeds [14] employed a nasal septal punch in dogs, and Swan and colleagues [29] used a rotary punch blindly applied through the wall of the atrium, creating an irregular defect that tended to close after several days. Swan commented that the procedure was difficult and unreliable because of the flexibility of the septum and constant motion of the heart. Dodrill [8] described a double-ringed clamp through which the atrial septum could be excised, but these defects also had a tendency to close within a month. Brodie and co-workers [4] modified the punch technique with a sharp, pointed trocar for puncture of the atrial septum and an outer sleeve to cut the septal defect, but 13% of the ASDs so created spontaneously closed. Rastan and Koncz [25] used a special septome with knives of varying diameters according to the size of the dogs, and later, the patients; 3 of 4 patients had excellent palliation, but the instrument never gained popularity, probably due to the need to blindly impale the atrial septum prior to excision. This factor, common to most of the procedures just mentioned, carries a high risk of perforating the posterior left atrial wall.

Although we do not know why these instruments have not attained general acceptance, it seems that they are too complex and have unpredictable long-term results. The Blalock-Hanlon surgical septectomy, which is still our "gold standard," produces a mortality of approximately 10% even today [7, 33]; hence, the need for an instrument which can render this operation simple and safe.

The instrument we have designed and tested appears to satisfy the necessary criteria of simplicity of form and use. It has two parts; introduction of each into the appropriate atrium assures the proper positioning of the septum and avoids the need for blind manipulation of a pointed instrument. The proper location of each part within the atrium is corroborated by palpation. The cutting cylinder is delivered to the baseplate by the guidepost, assuring accurate positioning of the cutting edge onto the baseplate. Further, it does not interfere with intracardiac circulation.

Seven of 44 animals died before they were scheduled to be killed, but only 1 animal (Group 2) appeared to have died as a direct result of this procedure (complete atrioventricular block). The others died of postoperative pulmonary complications, which are common to puppies postoperatively. Other possible complications such as air embolism and intraluminal thrombosis, as described by Swan and colleagues [29], were not experienced. A common difficulty attending previous septostomy instruments was the production of a slit-shaped defect that had a tendency to close. This may have been due to the fact that the septum often was just perforated, and not excised, by the instruments. Our device does not puncture, but excises part of the septum. It did this successfully in 42 of 44 puppies. In one of the two failures, we did not obtain septal tissue in the filter and immediately recognized the failure. In the second animal, we retrieved a piece of septum in the filter, but the defect was closed 218 days later, the only instance of late closure.

Although venae cavae–RA oxygen saturation step-ups are dependent on hemodynamics as well as the size of the ASD, we made these measurements simply to document that an increase did occur. The actual magnitude cannot be compared with those recorded with the Blalock-Hanlon operation in patients because the circulations are obviously different between normal puppies and patients with TGA. However, the data can be compared within each group: Group 2, with the larger adjoining holes, had a larger oxygen saturation step-up (12%) than the smaller, single holes in Group 1 (8%) or Group 3 (7%). The average diameter of the defects in the animals in Group 3 was greater, representing a 50% increase in defect area with animal growth since each was created with the same instrument. Therefore, it seems reasonable to assume that most surgically created ASDs not only remain patent but increase in size as the animal grows and develops. Few reports in the literature directly address the issue of the size of the ASD with TGA. Most authors note the size at operation or at postmortem examination, or indirectly from balloon size. Consequently, all are subject to question when used as a basis for measurement of the ASD initially created. In a clinical study of Rashkind's balloon atrial septostomy, Vlad and Lambert [32] reported that sustained excellent results were always associated with defects larger than 15 mm in diameter. They also mentioned that in rare instances, even very large defects (over 25 mm) are associated with inadequate aortic saturations. However, the majority of these defects were measured either at postmortem examination or operation, and usually months or years after actual creation of the defect. We believe that the defect size increased as the child grew and that the size of the defect created at the initial operation may have been significantly smaller, possibly in the 1 cm diameter range. Baker and associates [1] obtained the size of the ASD created with the Rashkind procedure by measuring the distended balloon that could be gently pulled through the defect, and stated that palliation is reliably achieved whenever the defect is greater than 12 mm in diameter. We maintain that this is the size of a temporarily "stretched" hole and that the defect may permanently return to a slightly smaller size. After examining several pathological specimens, it is obvious that the anteroposterior dimension of the true atrial septum in a 3 to 4 kg infant rarely exceeds 1.5 cm, and creation of a defect of the same size could be difficult and dangerous. We propose that creation of a clean-cut, symmetrical, properly located, round, 1 cm defect would provide egress for adequate shunting to occur. The instrument we have described here is able to do this predictably, simply, and safely in our experimental animals.

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Aortocoronary Bypass with Homologous Saphenous Vein: Long-Term Results

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ABSTRACT **Between February, 1973, and February, 1979, 27 homologous saphenous veins were used in 20 patients (mean age, 54 years). Seven fresh grafts were used less than 24 hours after severance. They were kept at a temperature of 4°C in saline solution containing penicillin. Twenty cryopreserved grafts were used within a period of eight days to 2 months from severance. They were preserved in glycerol at a temperature of −40°C.**

One patient (5%) died postoperatively. A perioperative myocardial infarction developed in 3 patients (15%). Average follow-up is 27 months. No late mortality was registered. Fifteen patients are free from symptoms, and 3 patients have residual angina with exercise.

Control angiograms were made in 13 patients 1 to 68 months after operation; 17 homografts were seen. Early occlusion of 1 graft and late occlusion of 8 grafts were registered.

The poor late patency rate does not seem to be related to either histocompatibility or technical conditions. Conversely, microscopic examination of several cryopreserved grafts showed that the mode of preservation resulted in deterioration of intimal and medial tissues of the vein. Therefore, it appears to us that the use of homologous saphenous veins should be avoided for coronary bypass.

Autologous internal saphenous vein is normally used for myocardial revascularization in patients with coronary disease. Clinical results are good, and reported late patency rates are high. Internal mammary artery can also be used with excellent results, but this procedure has been proved to have its anatomical and technical limits. In some patients, however, neither internal saphenous veins nor internal mammary artery is available. Hence, the use of fresh or preserved homologous saphenous veins has been suggested.

This study reports our experience of myocardial revascularization with homologous saphenous veins, with special reference to the late patency rate and to microscopic examination of cryopreserved grafts.

Material and Methods

Between February, 1973, and February, 1979, 1,289 patients were operated on for coronary disease. Twenty of them, 11 women and 9 men 40 to 67 years old (average age, 54 years), underwent 27 aortocoronary bypasses with homologous saphenous veins. Coronary operation was indicated in 19 patients for disabling angina resistant to medical therapy. Among these patients, 4 had significant (⩾ 70%) stenosis of one vessel, 6 had significant stenosis of two vessels, and 9 had lesions of three or more vessels. In 1 patient, a double coronary bypass was performed during repair of acute dissection of the ascending aorta with dissection of the left main coronary artery.

Homologous saphenous veins were anastomosed to the left descending coronary artery in 11 bypasses, to the circumflex artery in 9, and to the right coronary artery in 7. They were the only grafting material used in 13 patients (7 single, 5 double, 1 triple bypass). In the remaining 7 patients, homologous saphenous veins were associated with autologous veins (4 patients) or a polytetrafluoroethylene (PTFE) prosthesis (3 patients). Coronary arteries were considered suitable if they were greater than or equal to 2 mm at arteriography and at operation.

Use of homologous saphenous veins was indicated in 6 patients because of previous strip-

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Table 1. Clinical and Angiographic Results in Patients Receiving a Preserved Homologous Saphenous Vein and Undergoing Early or Late Coronary Arteriography

Patient No., Age (yr), Sex	Grafted Artery	Type of Graft	Angiography Date (mo)	Angiography Result	Symptoms
1. 61, F	RC	CP	68	Occluded	None
2. 59, M	Circ.	Fresh	44	Patent[a]	Angina
	LAD	Fresh		Occluded	
3. 40, M	Circ.	Fresh	32	Occluded	None
	RC	Fresh		Patent	
4. 47, F	Circ.	CP	31	Occluded	Pulm. emb.
5. 50, F	LAD	CP	12	Occluded	None
6. 53, M	RC	Fresh	11	Occluded	None
7. 55, F	RC	Fresh	8	Occluded	Angina
	LAD	Fresh		Occluded	
8. 60, M	LAD	CP	3	Patent	None
9. 44, M	Circ.	CP	2	Patent	None
10. 40, F	LAD	CP	2	Patent	None
	Circ.	CP		Patent	
11. 58, F	LAD	CP	1	Occluded	None
12. 64, F	RC	CP	1	Patent	Angina
13. 50, M	Circ.	CP	1	Patent	None

[a] Stenosed.

RC = right coronary artery; Circ. = circumflex coronary artery; LAD = left anterior descending coronary artery; CP = cryopreserved; Pulm. emb. = pulmonary embolism.

ping of internal saphenous veins. As for the other patients, autologous veins could not be used because of important varicosity or inadequate caliber (> 10 mm or < 3 mm). Homologous veins were severed from patients undergoing coronary or peripheral vascular operation, in whom they were not completely used. They were of good quality and adequate caliber.

Seven fresh homologous saphenous veins were used less than 24 hours after severance (fresh grafts). They were kept at a temperature of 4°C in saline solution containing 150,000 IU of penicillin per 100 ml of solution. Twenty homologous saphenous veins were used within a period of eight days to 2 months after severance (cryopreserved grafts). They were preserved in glycerol at a temperature of −40°C. Before use, the veins were rinsed with saline solution at 25°C for thirty minutes.

Results

One patient (5%) died of acute mediastinitis eleven days postoperatively. Postmortem examination revealed occlusion of the 3 implanted homologous grafts. A perioperative myocardial infarction developed in a grafted area in 3 patients (15%). An early control angiogram showed that the grafts were occluded. One was autologous, 1 was homologous, and 1 was a PTFE prosthesis.

The follow-up period for the 19 survivors ranges from 6 to 72 months (average follow-up, 27 months). There was no late mortality. Fifteen patients experienced no further angina and have a normal activity. Three patients suffer from residual disabling angina. One patient experienced late pulmonary embolism not related to the coronary disease.

Angiographic Results

Angiograms were made of the coronary arteries and the grafts in 13 patients over a period of 1 to 68 months following operation (Table 1). Seventeen homologous saphenous veins were visualized. Seven of them were checked at 3 months or less after operation (early control).

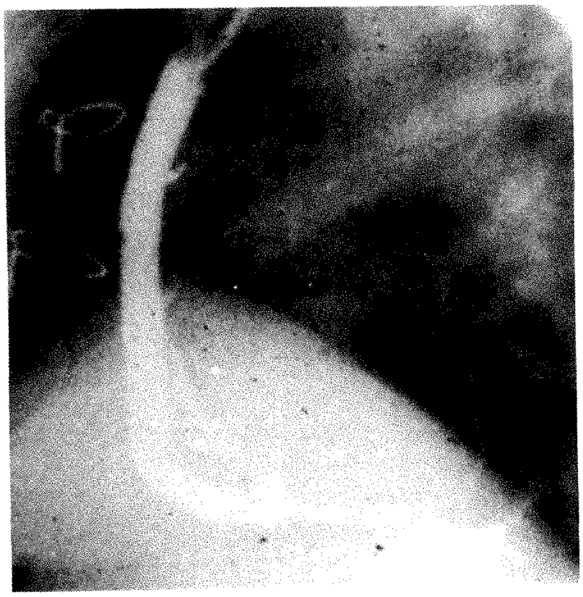

Fig 1. Cryopreserved saphenous vein homograft implanted on the right coronary artery. Angiographic control 1 month after operation.

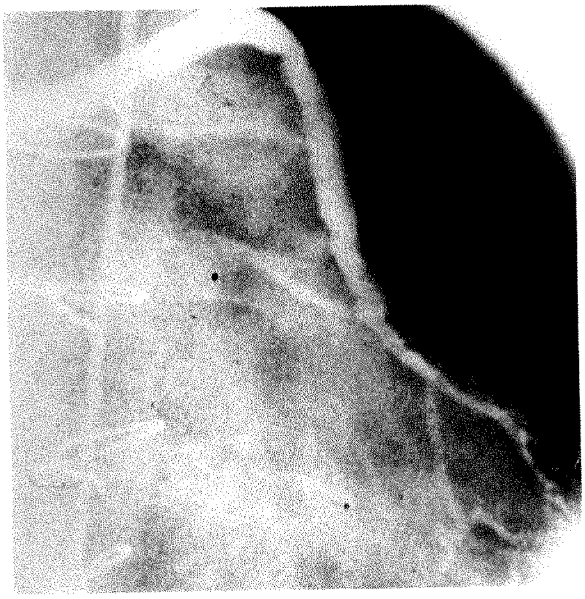

Fig 2. Cryopreserved saphenous vein homograft implanted on the circumflex coronary artery. Angiographic control 2 months after operation.

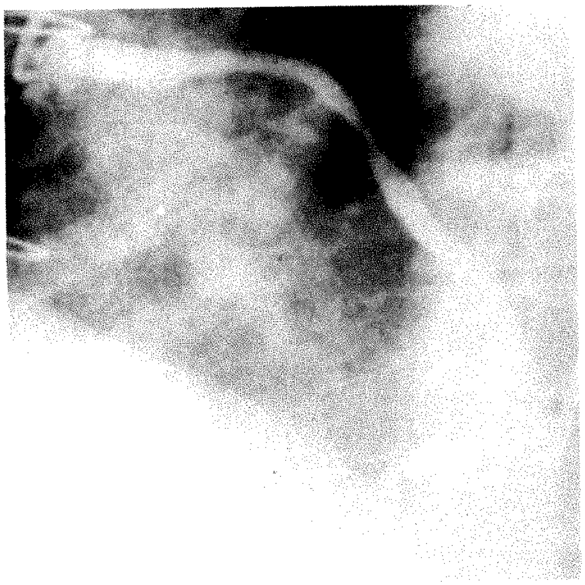

Fig 3. Fresh saphenous vein homograft implanted on the circumflex coronary artery. Angiographic control 44 months after operation. There is moderate stenosis of the graft.

Table 2. Results of Early and Late Control Angiograms according to the Mode of Graft Preservation

Graft	No. of Grafts	Early Control (< 3 mo)	Late Control (8 to 68 mo)
Fresh	7	. . .	Occluded, 5; patent, 2
Cryopreserved	10	Occluded, 1; patent, 6	Occluded, 3
Total occlusion rate		1/7 (14%)	8/10 (80%)

The other 10 were checked within 8 to 68 months following operation (late control).

Six out of 7 (86%) of the early-check grafts are patent (Figs 1, 2). Conversely, among the 10 grafts visualized later, 8 (80%) are occluded. One of the 2 patent grafts is moderately stenosed (Fig 3). Table 2 summarizes the angiographic results according to the mode of graft preservation.

Pathology

Several samples of homologous saphenous veins cryopreserved in glycerol at a temperature of −40°C were examined by electron microscopy. Duration of cryopreservation ranged from three to seven weeks. Samples were stabilized in glutaraldehyde at 2.5% and buffered with cacodylate. Then, fixation was achieved with osmium tetroxide. The samples were embedded in Epon prior to semithin and ultrathin cutting.

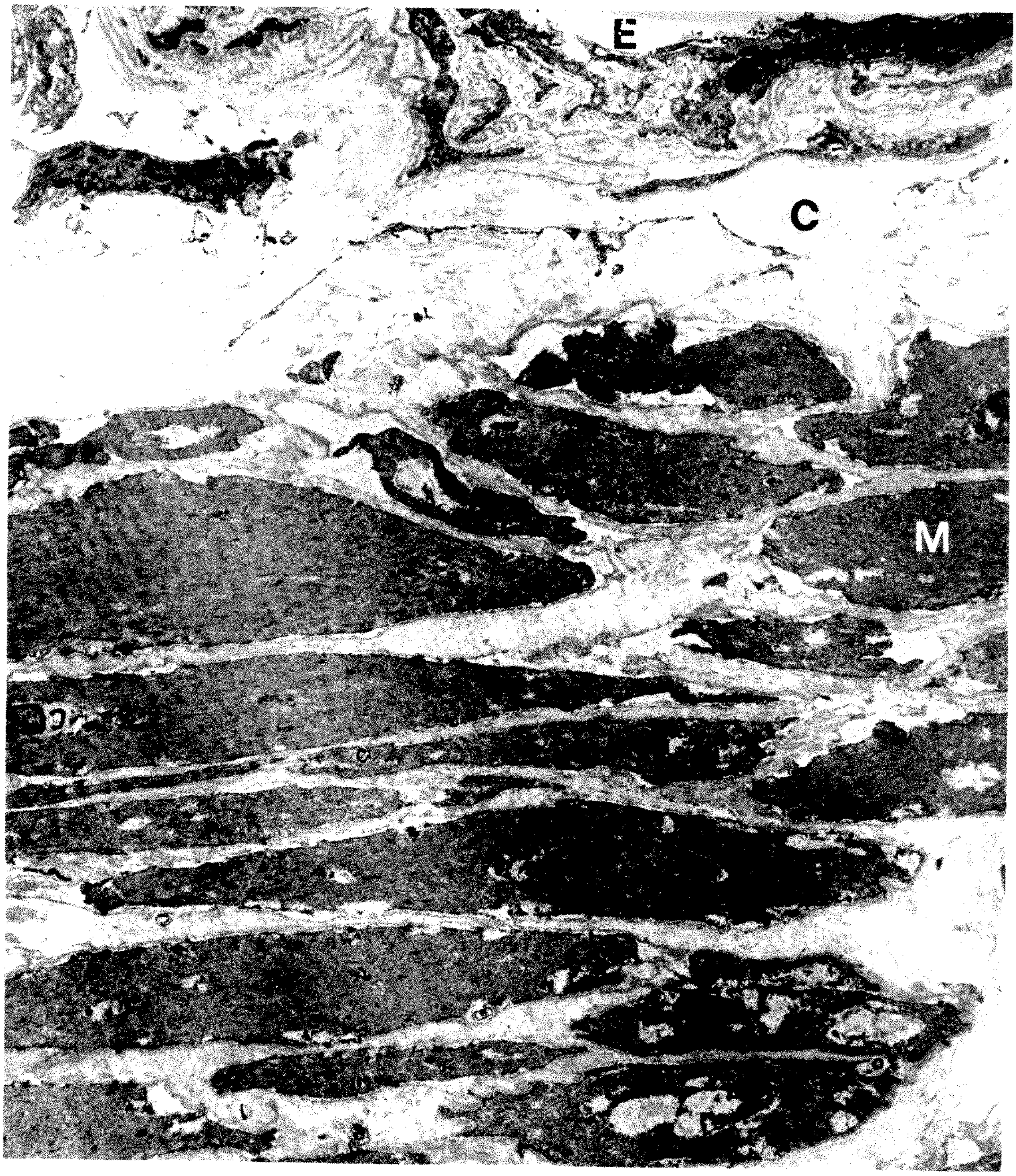

Fig 4. Histological alterations after three weeks of cryopreservation: endothelial necrosis (E); *alteration of connective frame* (C); *and myocytic lesions* (M).

Three types of alterations were observed (Fig 4). (1) In all samples, the endothelium was almost completely destroyed. (2) The connective frame was consistently altered, with dispersion of collagen fibrils, numerous cellular fragments, and rare elastic structures. (3) Myocytic alterations (cytoplasmic vacuolization, cytoplasmic retraction, nuclear densification) were always present but were of variable intensity.

Intensity of all histological lesions is dependent on the duration of cryopreservation, especially as regards the muscular structures of the vein (Fig 5).

Comment

Use of homologous saphenous veins as arterial grafting material is not really common. Clinical experience with fresh venous homografts used

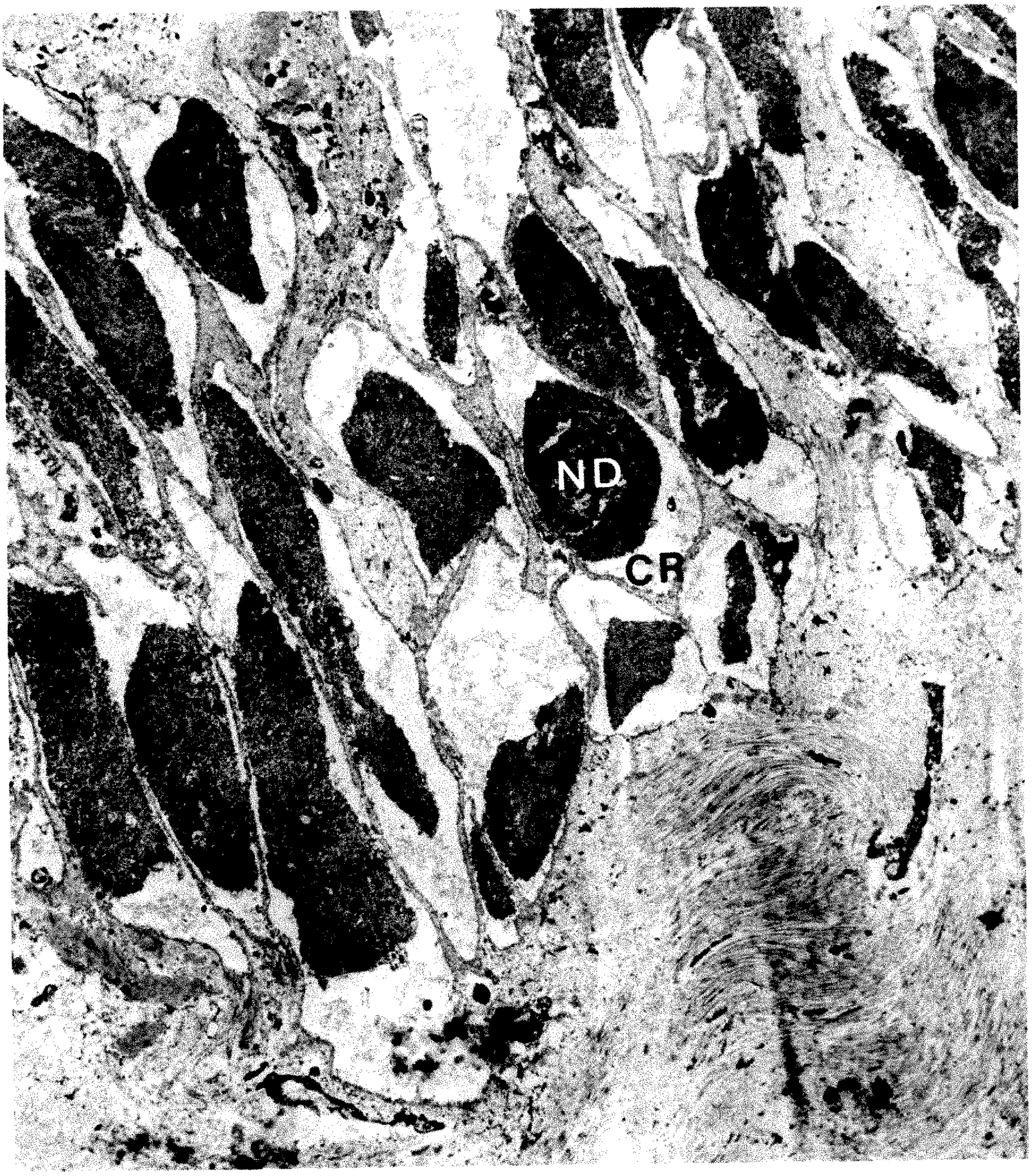

Fig 5. Myocytic alterations are more severe after seven weeks of cryopreservation. They consist of cytoplasmic retraction (CR) *and nuclear densification* (ND).

in peripheral vascular operations has shown a high rate of late occlusion, especially in the femoropopliteal position [10].

The role of histocompatibility has been discussed, but exact matching for blood group (ABO) compatibility does not seem to improve the late patency rate [9]. Therefore, cryopreservation has been suggested in order to eliminate or reduce antigenicity and, thus, improve late results [13]. In fact, the use of cryopreserved homografts as vascular material for chronic hemodialysis is quite satisfactory. But the importance of blood flow through the graft in this specific indication may explain the good late patency rate [11].

In spite of rapid developments in coronary operations, few studies have reported results of myocardial revascularization with homologous saphenous veins. In 1976, Tice and co-workers [14] reported a series of 13 patients who underwent aortocoronary bypass using cryopreserved homologous saphenous veins. Postoperative angiograms made within 1 to 42 months following operation demonstrated 6 out of 8 grafts to be patent. But only half the patients allowed angiography to be done, and the late mortality was particularly high in this series (30%).

In our early experience, homologous saphenous veins were used in preference to internal mammary arteries or other autologous substitutes because of their easy availability and because of the good initial reports [13] concerning this type of grafting material. However, our experience with homologous saphenous veins is paradoxically disappointing. Clinical results are good since 80% of the patients are symptom free several years after operation. But the late patency rate of homologous grafts is very low (20%) compared with that of autologous veins at one year (84%) [6]. The high occlusion rate can be explained by neither the poor quality of the coronary arteries nor the technical conditions. However, it could be due to either immunological rejection in the case of the fresh graft or morphological alterations resulting from cold in the case of the cryopreserved graft.

Experimental studies with fresh homografts implanted in animals show that rejection appears very early (from five to ten days following implantation). The first histological lesion consists of the morphological alteration of endothelial cells. Then, the muscle cells of the tunica media quickly degenerate and are replaced with connective elements [8, 12, 16]. The inflammatory reaction is initiated during the second month and the tunica adventitia is affected during the sixth month. After a year the graft is completely invaded by fibrosis, and the vein generally is occluded [7].

Cryopreservation in glycerol or dimethyl sulfoxide is supposed to eliminate antigenicity and, thus, rejection reaction [15]. This notwithstanding, one can observe histological lesions probably due to the mode of preservation since they are identical in autologous and homologous grafts [5]. These lesions, prevailing in the tunica media, seem to increase with the duration of cryopreservation [4, 5]. But it has been stated that, since histological alterations observed after crypreservation and implantation are very similar to lesions due to rejection, they could likewise be the result of an immunological reaction [3]. This hypothesis is contradicted by our study. The samples of homologous veins that we studied were only cryopreserved and not implanted. Since rejection reaction is, then, impossible, cold itself or the combination of cold and dehydration are responsible for histological alterations. It is of particular concern that only 3 cryopreserved grafts were studied late and that the fate of 10 of the others is completely unknown. It is conceivable that if all are patent, there could be a late patency rate for cryopreserved grafts of 77%, i.e., an acceptable patency. But, since the patients undergoing long-term control angiography were not selected according to the presence or absence of recurring symptoms, it seems reasonable to think that the occlusion rate of the cryopreserved grafts is the same in controlled and noncontrolled patients. Moreover, in the samples that were not implanted, the severity of histological lesions after only three weeks of cryopreservation leads us to presume that graft fibrosis and ultimate thrombosis should be the ineluctable fate of these arterial substitutes.

In order to avoid rejection reaction with fresh grafts or alterations by cold condition in cryopreserved grafts. preservation in glutaraldehyde has been suggested [1]. But it turns the vein into an inert material, the long-term patency of which is also rather uncertain.

The results of our experience of coronary operations using homologous saphenous veins suggest that this technique should be abandoned [2]. But finding good arterial substitutes when autologous saphenous veins are not available is not easy. At present, we suggest the following: (1) the use of internal mammary artery to bypass the left descending coronary artery, whenever possible; (2) the use of any convenient autologous vein, such as external saphenous vein or cephalic vein, whenever a free graft is required; and (3) the use of a prosthesis, such as a PTFE tube, for bypass of large arteries whenever no other arterial substitute is available.

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Discussion

DR. HENDRICK B. BARNER (St. Louis, MO): Eight of 10 grafts were occluded and the ninth was stenotic at angiographic follow-up 8 to 68 months after operation. These findings are consistent with published experimental data and clinical observations from the Ochsner Clinic, the University of Sidney, and our own institution concerning the use of allogenic vein in the femoropopliteal position.

Others have claimed that preservation of vein by freezing with glycerol or dimethyl sulfoxide may alter the antigenicity of the vein. However, the experimental studies of Perloff, Williams, Porter, and their associates document that the frozen vein is equally antigenic as the fresh vein and results in second-set rejection of skin grafts.

Porter and his co-workers have shown that glutaraldehyde treatment of the allogenic vein will abolish antigenicity. However, this results in a nonviable graft that may predispose to aneurysmal degeneration. Yesterday I spoke with Dr. Porter. He expressed great concern about the long-term durability of the glutaraldehyde-treated allogenic vein, and would be unwilling to use this material in the aortocoronary position.

I ask the authors about the necessity for use of this conduit. In our experience with 2,400 patients having coronary artery bypass grafting, we have never lacked autogenous conduit. When greater saphenous vein has been inadequate, it occasionally has been necessary to utilize the lesser saphenous, cephalic, or basilic veins as well as the internal mammary artery. One of my concerns is that availability of an alternative and readily accessible conduit may encourage the surgeon to accept an inferior conduit rather than scramble a little to procure autogenous tissue.

The authors should be congratulated for bringing their objective data to our attention. I hope they convinced all of us that allogenic vein is a bad conduit for coronary reconstruction.

DR. JOGINDER N. BHAYANA (Buffalo, NY): I enjoyed Dr. Bical's paper, but our results are at variance with those just reported. Over the last five years at the Veterans Administration Medical Center in Buffalo, we have operated on more than 800 patients with coronary artery disease. There were 7 patients from whom we could not obtain any autogenous tissue for coronary bypass grafting. For these patients, we used preserved homograft veins. Veins were stored in sterile bottles containing 100 ml of Plasmanate and 0.5 gm of Keflin (cephalothin sodium). Each bottle was sealed with tape; the length of vein and the blood group were noted on the outside. The bottles were stored at −60°C for a period of up to 6 months.

There were 7 patients in this group ranging from 52 to 60 years old. All had triple coronary artery disease, and a total of 25 coronary bypass grafts were done (3.6 grafts per patient). In the follow-up period, extending up to 52 months, 1 patient died of ventricular arrhythmia a month after operation. Postoperative angiograms were made for all survivors 4 to 12 months following operation. Early graft patency has been 86% (19/22).

I think our results differ from those just presented for the following two reasons: Dr. Bical included the fresh and cryopreserved grafts together; and ABO compatibility between the donor and recipient has not been taken into consideration. In our series, the donor and recipient had the same blood group.

DR. NOEL L. MILLS (Jefferson, LA): I congratulate Dr. Bical and his group on a fine paper, which certainly contributes, although in a negative way, to our search for a substitute graft. At the Ochsner Clinic, we have used homologous saphenous vein grafts for reconstruction of tibial, peroneal, subclavian, and brachial arteries, systemic-pulmonary shunts, and hemodialysis access as well as aortocoronary bypass. Our longest patent graft has been in place for eleven years.

Homografts from living related donors frozen to −40°C overnight have performed best. Freezing has reportedly decreased antigenicity, although this is still controversial. Glutaraldehyde-tanned grafts are difficult to work with and offer no advantage. Our experience with the fison-digested grafts is small. An attempt is made to match ABO groups, and this is rigidly adhered to whenever we use fresh, nonfrozen grafts.

Hypertension adversely affects results, and we have seen late aneurysm formation only in hypertensive patients. Shorter grafts fare better than longer segments. Larger diameter grafts have a higher patency than small grafts and in fact, homografts with an internal diameter smaller than 5 mm should not be used.

These homologous vein grafts are used as "salvage" procedures to buy time. Although we do maintain a vein bank for those patients for whom we have no alternatives, we believe that because of the many variables connected with their use, the fate of the homograft veins is really unpredictable at present.

I wonder if Dr. Bical can give us some guidelines. One, is there a time limit from the time of death for harvesting the vein if you use cadavers? Two, are donors heparinized? Three, do you make any attempt to match major ABO groups or to control antigenicity by altering the immune response with drugs?

DR. BICAL: I thank the discussants for their comments. Antigenicity is eliminated or at least reduced by glycerol. We presume that since histological alterations exist before implantation, cryopreservation is responsible for degeneration and occlusion of the vein. I agree with Dr. Barner that glutaraldehyde certainly eliminates antigenicity, but by tanning the tissues it turns the grafts into a nonviable substitute.

Regarding Dr. Bhayana's question, there is no difference in occlusion rate between fresh and cryopreserved homografts, but the number of grafts is too small to be significant. I think a long-term follow-up is necessary to evaluate the results of homograft.

Concerning Dr. Mills's questions, we did not attempt to match the ABO group when fresh homografts were used, and we did not think it necessary with cryopreserved grafts. Second, we did not use cadaver veins but only remaining veins following surgical procedures in other patients. Last, we never gave an immunosuppressant to the patients.

Suppression of Renin Production in Patients Undergoing Coronary Artery Bypass

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ABSTRACT **Twenty patients undergoing elective myocardial revascularization for coronary insufficiency were divided into two equal groups. In 10 patients, propranolol was discontinued 24 hours before operation while the remaining patients received propranolol until the day of operation. Plasma renin was elevated in the intensive care unit in the control group ($p < 0.05$) whereas patients receiving propranolol did not demonstrate significant elevation of plasma renin. Systemic vascular resistance was elevated in both groups in the intensive care unit ($p < 0.05$) and was associated with hypertension as defined by a blood pressure of ≥ 160/100 mm Hg in 80% of the control patients and 70% of patients receiving propranolol. We conclude from this study that renin metabolism does not contribute significantly to the production of hypertension following coronary artery operation.**

The early postoperative period after myocardial revascularization is frequently complicated by transient hypertension [10, 15, 18, 22, 25]. Elevation of plasma renin has been observed following coronary artery operation and is associated with increased systemic blood pressure [18, 25]. This study reports the relationship between postoperative hypertension and plasma renin in patients receiving propranolol.

Materials and Methods

The study consisted of 20 patients undergoing elective myocardial revascularization for coronary insufficiency. No effort was made to select patients for the study as long as they met the minimum requirements of the protocol. The protocol was designed to include all elective admissions for coronary artery operation except those patients with a previous history of hypertension and patients taking medications in addition to propranolol, isosorbide dinitrate, and nitroglycerin. Patients taking additional medications were excluded because of the known influence of many of the routine cardiac drugs on the renin-angiotensin system [6].

Propranolol was tapered in 10 patients following admission to the hospital 72 hours before operation and discontinued 24 hours prior to operation. The other 10 patients continued propranolol until the day of operation.

Screening biochemistry included a complete blood count, electrolytes, blood urea nitrogen, creatinine, and liver function tests. Baseline renin samples were drawn at 1400 hours the day before operation.

The entire group received a similar anesthetic protocol consisting of pentobarbital, 100 mg at bedtime and 2 hours preoperatively, and morphine sulfate, 10 to 15 mg 1 hour preoperatively. Additional morphine analgesic was not administered during the operative period. Induction was carried out with thiopental and pancuronium bromide, 0.1 mg per kilogram of body weight, and anesthesia was maintained with oxygen, nitrous oxide, and halothane. No inotropic agents were used during the operation or in the postoperative period to assist cardiac output or maintain systemic blood pressure.

During induction, an arterial line was inserted into the radial artery and a Swan-Ganz thermodilution catheter was positioned in the pulmonary artery. Cardiac output was then determined with the Edwards Model 9510-A computer utilizing injections of ice-cold saline solution. Peripheral vascular resistance was calculated from the following formula:

$$\text{PVR} = \text{Mean arterial P} - \text{Mean atrial P} \times 1333/\text{CO}$$

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Patient-Profile

Group	Age (yr)	Propranolol (mg/q.6 h.)	No. of Grafts per Patient	Bypass[a] (min)	Hypothermia[a] (min)
Controls	36–64 ($\overline{58.6}$)	40–100 ($\overline{52}$)	2.9	131.7 ± 10.6	94.7 ± 6.9
Propranolol	51–66 ($\overline{57.7}$)	40–100 ($\overline{53}$)	3.0	121.5 ± 12.7	81.7 ± 11.8

[a] ± Standard error of the mean.

where PVR = peripheral vascular resistance (dynes sec cm^{-5}), P = pressure (mm hg), and CO = cardiac output (milliliters per second). After completion of the induction phase, arterial samples were drawn for a complete blood count, electrolytes, and plasma renin. Further arterial samples and cardiac outputs were obtained at thirty minutes and 1 hour on bypass and 2½ and 5 hours after bypass. (Cardiac output was calculated on bypass from pump flows of 2.51 $L/m^2/min$).

Nonpulsatile cardiopulmonary bypass with moderate hypothermia to 28°C was maintained with a roller pump and a standard bubble oxygenator. Perfusion pressure on bypass ranged between 60 and 80 mm Hg. Hypotension was corrected with the addition of Plasmalyte solution (Travenol) or by administering small doses of Neo-Synephrine (phenylephrine hydrochloride).

The operative technique was similar in each patient. After cardiopulmonary bypass was established, the patient was cooled to 28°C. The aorta was cross-clamped, and the aortic root was perfused with cold potassium cardioplegic solution. The distal coronary anastomosis was then carried out. Additional cardioplegia was infused every twenty minutes or sooner if electrical activity was observed. Following completion of the distal grafts, the aortic cross-clamp was removed and the patient was rewarmed. Proximal anastomosis was completed with the heart beating and with the aid of a partially occluding aortic clamp. Saphenous vein grafts were used in each patient.

Renin was analyzed by a modification of the Sealey method.* Arterial samples for plasma renin determination were injected into precooled glass tubes and placed on ice. The specimens were then immediately transported to the laboratory, spun down in a cold centrifuge, and frozen to −20°C.

Statistical significance was determined with the Student t test and the chi-square test with Yates' correction for small samples. All results have been reported as mean values with associated standard error.

Results

The Table illustrates the patient-profile of the two groups. There was no statistical difference between the two groups with respect to age, number of grafts per patient, dosage of propranolol, or duration of operation.

Plasma Renin

The results of plasma renin studies are illustrated graphically in Figure 1. Baseline renin assay 24 hours before operation was similar in both patient groups. During induction, the control patients and those patients receiving propranolol demonstrated a slight but not significant increase in renin activity. Throughout the period of extracorporeal circulation, there was no significant renin release in either group. Two and one-half hours after bypass, the control group demonstrated significant elevation of plasma renin in comparison with preoperative determination ($p < 0.05$, Student's t test) whereas patients receiving propranolol failed to demonstrate any change in renin activity.

Peripheral Vascular Resistance

Calculated systemic resistance is portrayed by bar graph in Figure 2. Vascular resistance increased significantly in the intensive care unit 2½ hours after bypass ($p < 0.05$, Student's t test) but was similar in both groups. Five and one-half hours after bypass, systemic resistance

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*New England Nuclear, Radioimmunoassay Kit, Angiotensin 1, Billerica, MA.

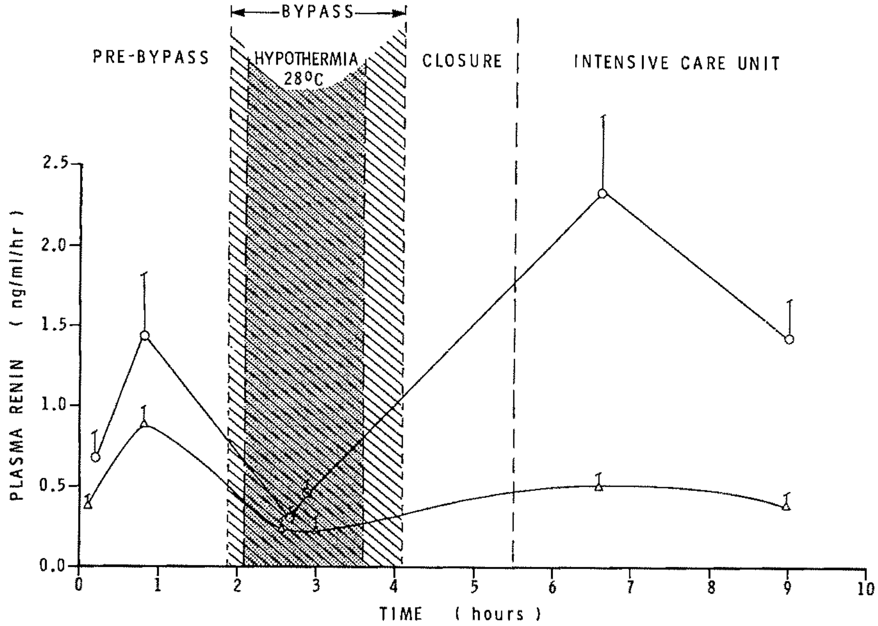

Fig 1. Plasma renin concentration during cardiopulmonary bypass with hypothermia to 28°C in patients undergoing myocardial revascularization. (o = controls; Δ = patients receiving propranolol; ⁄{ = standard error of the mean.)

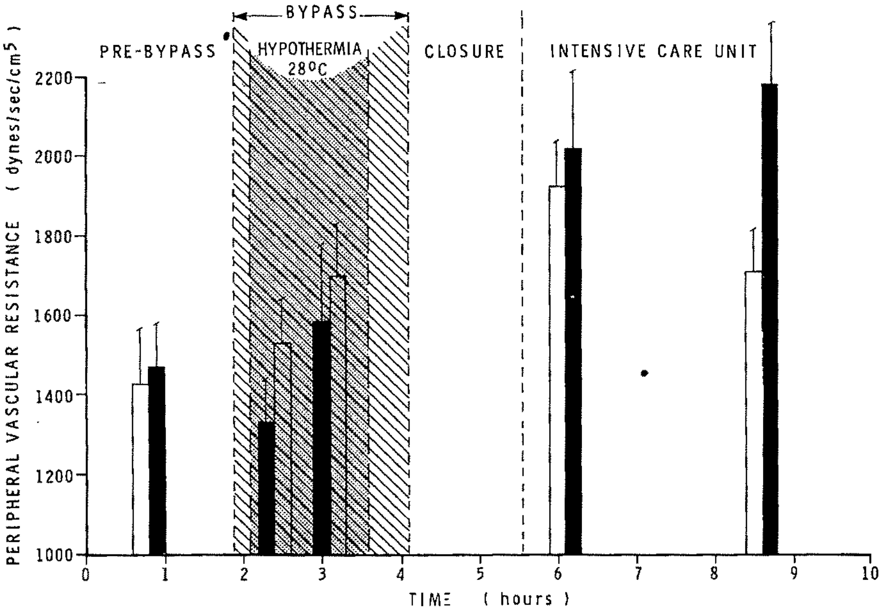

Fig 2. Peripheral vascular resistance during cardiopulmonary bypass with moderate hypothermia to 28°C. (■ = patients receiving propranolol; □ = controls; ⁄{ = standard error of the mean.)

tended to be higher in those patients receiving propranolol although the difference was not statistically significant. The reason for this difference in systemic resistance is not readily apparent. The data are difficult to interpret at this time because the majority of patients had experienced multiple postoperative interventions for the control of systemic hypertension. These interventions included regulation of intravenous fluids, varying amounts of sedation, and infusions of sodium nitroprusside.

Hypertension

All patients were normotensive preoperatively and during operation. Following transfer to the intensive care unit, hypertension as defined by a blood pressure of ≥ 160/100 mm Hg and persisting for more than thirty minutes was observed in 80% of the control group and 70% of those patients receiving propranolol. The difference was not statistically significant (chi-square test).

Comment

Coronary artery operations have been associated with a high incidence of postoperative hypertension [10, 15, 18, 22, 25]. Elevated systemic blood pressure results in increased afterload and may contribute directly to the production of subendocardial ischemia and low cardiac output following myocardial revascularization [2, 3].

Previous studies [18, 25] demonstrated increased plasma renin following coronary artery operation and implicated the renin-angiotensin system in the production of postoperative hypertension. There appears to be a direct temporal relationship between the onset of postoperative hypertension and elevated systemic vascular resistance [18, 22]. The etiology of the increase in systemic resistance is obscure although nonpulsatile flow, hypothermia, and elevated plasma norepinephrine appear to be contributing factors.

Cardiopulmonary bypass is usually maintained with roller pumps delivering nonpulsatile flow. This method of extracorporeal circulation results in significant elevations of systemic vascular resistance [9, 17, 26]. Improved end-organ function associated with lowered vascular resistance has been reported with pulsatile flow [9, 17, 18, 26]. In a previous paper [18], we reported that patients receiving pulsatile perfusion during myocardial revascularization had less postoperative hypertension and lower systemic vascular resistance. Perfusion techniques for this study and in earlier papers [10, 15, 22, 25] utilized nonpulsatile circulatory support, which may have contributed to the production of postoperative hypertension.

Core hypothermia is a well-recognized method of myocardial protection during ischemic arrest [1]. Hypothermia alone causes a marked increase in systemic resistance [21, 28, 29]. Chen and Chien [8] attributed the elevated resistance in part to increases in blood viscosity and vascular hindrance. Although rewarming is accomplished prior to the end of bypass, we commonly observe patients with increased systemic resistance to be cold and peripherally vasoconstricted and have rectal temperatures in the range of 35° to 37°C on arrival in the intensive care unit.

In an earlier study [18] we observed high circulating levels of norepinephrine during cardiopulmonary bypass and in the early postoperative period. Circulating norepinepherine acts predominantly on alpha receptors [14] and is directly associated with elevated systemic vascular resistance.

Propranolol has been the drug of choice for control of the anginal syndrome in most patients with coronary insufficiency, and beta blockade has been used to suppress renin release in patients with renin-dependent hypertension [5, 16, 19, 27]. In this study we have reported the effects of beta blockade on renin activity and the incidence of hypertension following coronary artery operation.

Preoperative plasma renin activity was similar in both groups of patients although it tended to be lower in those patients receiving propranolol. These data correlate with previously reported renin activity in normotensive resting subjects [5–7]. That there was no statistical difference in the renin activity between those patients receiving propranolol and the control group probably reflects the small size of the sample population. The other possibility to explain the small difference in preoperative renin activity between the two groups could be related to residual beta blockade in the control patients. Residual blockade is doubtful, however, considering that propranolol was tapered 72 hours before operation in the control group. Previous reports have demonstrated unequivocally that propranolol is rapidly excreted and metabolized [11, 12] and that residual blockade is not present after 48 hours [13]. Further support for the lack of propranolol effect in control patients is supported by the observation that renin activity increased fourfold in these patients following operation.

Neither group demonstrated significant renin release during cardiopulmonary bypass. The absence of renin activity during circulatory support is related to the physiology of renin metabolism during open-heart operation. Schaffenburg and colleagues [23] showed that renin activity may be decreased as much as 700-fold by lowering the temperature from 37°C to 0°. Core hypothermia is a well-recognized method of myocardial preservation and was utilized in all our patients. Furthermore, 90% of the converting enzyme required for the conversion of angiotensin I to the active peptide angiotensin II is found in the lungs [20, 24] and is effectually removed from the circulating angiotensin I with the onset of extracorporeal circulation.

Our data indicate that plasma renin release was suppressed in the intensive care unit in those patients receiving propranolol. However, both groups of patients demonstrated similar elevations of systemic blood pressure and vascular resistance in the intensive care unit in the immediate postoperative period 2½ hours after bypass. Therefore, we must infer from these results that the renin-angiotensin system does not contribute significantly to the production of hypertension following aortocoronary bypass operation.

We conclude that despite increased renin activity in some patients following coronary artery operation, renin metabolism does not appear to be directly related to elevated blood pressure in the early postoperative period.

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Discussion

DR. TIMOTHY J. GARDNER (Baltimore, MD): In collaboration with our cardiology group, my colleagues and I recently looked at a group of patients in the early postoperative period following coronary artery bypass grafting. Of the 52 patients studied, about one-half had been continued on their usual propranolol dose up to the time of operation. The remaining patients had propranolol tapered and then stopped during the two days prior to operation. The incidence of hypertension in this group was between 65 and 70% and was actually slightly higher in the propranolol-treated patients than in those in whom propranolol had been stopped.

Serum analysis in these patients revealed elevated catecholamine levels in all patients with only minimal elevation of plasma renin. One conclusion from this brief study is that the mechanism of hypertension in propranolol-treated patients may be unopposed alpha-adrenergic stimulation in patients who are already beta blocked.

Coronary Embolism: Surgical Management

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ABSTRACT **The successful use of Fogarty catheter embolectomy combined with aortocoronary vein bypass graft in 4 patients with an acute myocardial infarction is presented. Three patients sustained acute occlusion of the coronary artery secondary to an embolus during cardiac catheterization. In the fourth patient, the left anterior descending coronary artery was occluded with a fragment of calcium debris during aortic valve replacement. All patients survived the operation.**

Acute occlusion of the coronary artery secondary to an embolus is uncommon, but its early recognition and appropriate surgical management may be lifesaving.

Before the advent of coronary arteriography and valve operations, coronary embolism was a rare finding and was associated primarily with bacterial endocarditis. Today, with the increased application of coronary arteriography and the performance of valve replacements, coronary embolism has become a clinical consideration.

The etiology of coronary artery embolism is varied. Bacterial endocarditis and intracardiac mural thrombus or neoplasm can cause acute coronary occlusions when detached fragments lodge in one of the coronary branches. In most of these cases, the patient sustains a fatal acute myocardial infarction, and the embolus is a postmortem finding.

Embolism during coronary arteriography has become well recognized. Of the reported instances of coronary artery bypass grafts done during acute myocardial infarction, many were performed in patients who sustained an acute embolic coronary artery occlusion in the cardiac catheterization laboratory [1–8]. The possibility of a calcific embolus during aortic valve replacement for calcific aortic stenosis has to be considered if signs of an acute myocardial infarction develop. Recognition of the process is vital since immediate therapeutic action may be lifesaving.

We report here the cases of 4 patients in whom saphenous vein aortocoronary bypass was employed in combination with Fogarty catheter embolectomy for acute coronary occlusion secondary to embolism.

Material

This series includes 3 men and 1 woman ranging from 51 to 68 years old (Table). Acute coronary occlusion developed in 3 patients while they were undergoing coronary arteriography, 2 by the Judkins technique and 1 by the Sones technique. This complication has been reported more frequently with the Judkins technique [7, 8]. All 3 patients had symptoms of severe, unrelenting chest pain. In 1, ventricular tachyarrhythmia and cardiogenic shock developed immediately following the onset of chest pain. Since these 3 patients were in the process of undergoing coronary arteriography, the anatomy of the acutely occluded coronary artery could be precisely depicted.

One of the 4 patients was undergoing aortic valve replacement for calcific aortic stenosis. When the patient was weaned from cardiopulmonary bypass, minimal blood flow was evident in the left anterior descending coronary artery (LAD), and the anterior myocardium demonstrated poor contractility. Following embolectomy, blood flow was restored in the vessel and normal color returned to the myocardium.

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Summary of Clinical Data on Patients with Acute Coronary Occlusion Treated with Fogarty Embolectomy and Coronary Bypass

Patient No., Sex, Age (yr)	Clinical Setting	Symptoms	Time of Acute Occlusion	Pathology	Operation Performed	Follow-up
1. F, 64	Preinfarction angina	Impending infarction	During catheterization (Judkins)	Catheter embolus	RCA embolectomy, AC bypass	Died 2 yr postop of cancer of kidney
2. M, 68	Preinfarction angina	Impending infarction, cardiogenic shock, ventricular fibrillation	During catheterization (Sones)	Catheter embolus	LAD embolectomy, AC bypass, RCA bypass	Asymptomatic 4½ yr postop
3. M, 53	Preinfarction angina	Impending infarction	During catheterization (Judkins)	Catheter embolus	LAD embolectomy, AC bypass	Restudied 2 mo postop: patent graft and LAD; alive 7 yr postop
4. M, 51	Calcific aortic stenosis	Pump failure; low cardiac output syndrome	During aortic valve replacement	Embolus of calcific debris	Aortic valve replacement, LAD embolectomy, AC bypass	No angina 8 mo postop

RCA = right coronary artery; AC = aortocoronary; LAD = left anterior descending coronary artery.

Case Reports

Patient 1

A 64-year-old woman was admitted with accelerating angina. A coronary arteriogram was performed by the Judkins technique and revealed normal LAD and circumflex coronary artery systems. Difficulty was encountered on cannulating the right coronary artery (RCA). An injection in the sinus of Valsalva revealed a 70% obstruction of the RCA proximal to the takeoff of the acute marginal branch; distally, the vessel was patent, but not well visualized. After the catheters were changed and after a repeat attempt was made to cannulate the right coronary ostium, severe constant chest pain developed. Repeat injection of the RCA revealed total occlusion of the artery at the posterior descending bifurcation. An electrocardiogram revealed posterior wall ischemia as evidenced by a 3 mm S-T segment depression in V_1 through V_3. Persistence of chest pain and electrocardiographic changes prompted the diagnosis of acute myocardial infarction, and the patient underwent operation.

Examination of the heart at operation revealed a fresh myocardial infarction in the posterior wall as evidenced by bluish discoloration and the absence of muscular contraction. Upon palpation of the RCA, a thrombus was noted at the takeoff of the posterior descending branch of the distal RCA.

Under cardiopulmonary bypass, the RCA was incised longitudinally proximal to the takeoff of the posterior descending branch. No backflow was evident at this level. A No. 3 Fogarty catheter was passed distally, and a 1.5 cm thrombus was extracted with the reestablishment of strong backflow. An aortocoronary saphenous vein bypass graft was then performed to the area of the arteriotomy on the RCA.

Immediate improvement of the color and contractility of the posterior wall was evident upon completion of the bypass graft. The patient tolerated the procedure well, and the electrocardiogram reverted to normal postoperatively. The patient died 2 years later of carcinoma of the kidney.

Patient 2

A 68-year-old man, a Jehovah's Witness with a history of accelerating angina, underwent cardiac catheterization by the Sones technique. The coronary arteriogram revealed multiple obstructions of the RCA with good runoff. Left main coronary, LAD, and circumflex coronary arteries were normal during three injections of the left system. During the last left coronary injection, the LAD was noted to have 100% proximal occlusion with no distal filling. Severe chest pain, hypotension, and ventricular fibrillation developed immediately. Resuscitation measures included defibrillation, vasopressors, and the intraaortic balloon pump. The patient was thought to have had an acute myocardial infarction with cardiogenic shock following "catheter-induced embolization." Emergency operation was undertaken.

The patient was immediately placed on cardiopulmonary bypass and cooled to 28°C. What was thought to represent an embolus was palpated in the proximal portion of the LAD. An arteriotomy was performed at that site, and a No. 3 Fogarty catheter was placed proximally and the thrombus removed. An aortocoronary saphenous vein bypass was performed to the arteriotomy site on the LAD and also the distal RCA. Marked improvement of the contractility and coloration of the anterolateral wall was noted. The patient was weaned from cardiopulmonary bypass without incident. Graft flows were measured at 60 ml per minute (LAD) and 90 ml per minute (RCA) without support from the intraaortic balloon pump. Postoperatively, electrocardiograms revealed no evidence of infarction.

The patient's postoperative course was later complicated by acute upper gastrointestinal bleeding for which emergency vagotomy and pyloroplasty were performed. The remainder of his hospitalization was uneventful, and he remains totally asymptomatic 4½ years later.

Patient 3

A 53-year-old man was seen with a 3-year history of recurrent angina. While the patient was undergoing diagnostic workup, symptoms consistent with unstable angina developed. An electrocardiogram revealed ventricular irritability, but no evidence of ischemia. Cardiac catheterization was performed. The first injection of the LAD revealed a nonocclusive obstruction at the level of the first septal perforator, but repeat injections revealed total proximal occlusion of the artery. Concomitant with the change on the coronary arteriogram, severe, unrelenting chest pain and dyspnea developed. Diagnosis of acute occlusion of the LAD was made, and the patient underwent emergency bypass.

Examination of the heart revealed the apex of the left ventricle to be distended, cyanotic, and noncontracting. The LAD was palpated, and a cordlike obstruction was noted in the proximal portion of the vessel extending to the level of the first septal perforator. The distal portion of the vessel was not distended. An arteriotomy was performed at the level of the occlusion, and a No. 3 Fogarty catheter was passed proximally and distally. A disorganized clot was extracted from both directions, and strong antegrade flow and backflow were reinstituted. Aortocoronary saphenous vein bypass was performed to the LAD at the level of the arteriotomy. The infarcted area of the ventricle was observed for some time, and dramatic improvement in color and contractility was noted.

Postoperatively, the patient's electrocardiograms showed no evidence of infarction. He continued to complain of intermittent chest pain following operation and underwent repeat catheterization, which revealed a patent graft as well as a patent LAD. The patient continues to do well, although he has mild symptoms of angina, 7 years after emergency bypass.

Patient 4

A 51-year-old man was seen with a three-month history of recurrent, nonexertional angina, palpitations, and one episode of syncope. Cardiac catheterization revealed severely calcific aortic stenosis and mild regurgitation. The peak to peak gradient across the aortic valve was 115 mm Hg. Moderate left ventricular hypertrophy was noted. Coronary arteriograms were normal.

The patient was operated on on a semiurgent basis and underwent aortic valve replacement (No. 21 Björk-Shiley aortic prosthesis). Perfusion of the LAD was instituted immediately following aortotomy, and flow was measured and recorded at 400 ml per minute. A bicuspid aortic valve had extensive calcifications involving the entire aortic annulus and anterior leaflet of the mitral valve. These were debrided meticulously by means of sharp dissection and rongeur. Following debridement, perfusion of the RCA was performed, with flows measured at 600 ml per minute.

When the patient was weaned from cardiopulmonary bypass, the anterior wall of the myocardium was not contracting well (as it had initially), and absence of blood flow in the LAD was noted. Because it was thought that acute embolic occlusion of the LAD by calcific debris had occurred, cardiopulmonary bypass was reestablished. An arteriotomy was performed in the LAD at the junction of the middle and distal thirds of the vessel. A No. 3 Fogarty catheter was passed proximally and distally, and a small piece of calcific debris was recovered. Forward flow and backflow strikingly improved. Aortocoronary saphenous vein bypass was then performed to the arteriotomy in the LAD.

Postoperatively, the patient had postpericardiotomy syndrome, but otherwise did well. Electrocardiograms showed no evidence of infarction postoperatively, and the patient remains asymptomatic eight months later.

Results

Of the 3 patients in whom acute infarction developed during cardiac catheterization, 1 died of an unrelated cause 2 years postoperatively. The second patient in this category is totally asymptomatic 4½ years after operation. It was in this patient that cardiogenic shock developed prior to emergency bypass. The third patient had a patent graft two months later. He continues to be followed 7 years later and is doing well. The follow-up on the last patient is eight months. He is asymptomatic.

It should be noted that the 4 patients who were operated on within six hours of acute coronary embolism did not have signs of an acute myocardial infarction postoperatively.

Comment

The consequences of an acute coronary embolism were analyzed by Roberts [9]. He concluded that the outcome depends on two factors: the size of the embolus and the original size of the artery in which it becomes lodged. A very small embolus may be clinically silent. A large embolus will lodge in a large coronary artery and result in myocardial necrosis or a fatal ventricular arrhythmia.

Another important factor is the status of the coronary arteries preceding the embolism. In Patients 1 and 3, the coronary arteries embolized were already obstructed significantly. In Patient 3, the embolus was impacted at the level of the obstruction at the beginning of the LAD, thereby producing a large area of acute ischemia and resulting in ventricular fibrillation.

In Patient 4, since the aortic valve was severely calcified, it was safe to assume that a piece of calcium had embolized at that level. The assumption was confirmed after the artery was opened and the embolus removed.

The successful use of Fogarty embolectomy [10] combined with saphenous vein aortocoronary bypass is illustrated in these 4 patients. The application of this technique is especially useful in instances of acute coronary artery occlusion during cardiac catheterization when the anatomy of the occluded coronary is known and when immediate myocardial revascularization with removal of the embolus can be accomplished. Our 4 patients who were operated on within six hours of embolization did not have signs of acute myocardial infarction postoperatively. Other clinical settings in which this technique can be of the utmost value are during aortic valve replacement when calcific debris might embolize and during repairs of the ascending aorta when manipulation of mural thrombus might cause a coronary embolus to lodge at the origin of the LAD.

We conclude that Fogarty embolectomy coupled with saphenous vein aortocoronary bypass should be employed in those instances of documented acute coronary occlusion secondary to embolism. Myocardial revascularization will reduce the infarct size and may reverse the ischemic process if performed within six hours of acute ischemia [8]. Though coronary flow would be improved by coronary bypass alone, embolectomy prevents the possibility of peripheral dispersion of the thrombus and may restore flow to small branches arising in the area of the impacted clot.

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Transaxillary Pleurectomy for Treatment of Spontaneous Pneumothorax

Jean Deslauriers, M.D., Maurice Beaulieu, M.D.,
Jean-Paul Després, M.D., Michel Lemieux, M.D.,
Jacques Leblanc, M.D., and Marc Desmeules, M.D.

ABSTRACT **In the 16-year period 1962 to 1978, 409 transaxillary apical pleurectomies were carried out for definitive treatment of spontaneous pneumothorax in 362 patients. Surgical indications included recurrence (336), bilaterality of the disease (23), persistent air leak (22), and nonexpansion of the lung (10). There was 1 operative death (unsuspected brain tumor), and 3 patients required reexploration for clot removal. The average postoperative period of hospitalization was 6 days. Three hundred ten patients (86% of all patients) were contacted for follow-up 1 to 16 years after operation (average, 4.5 years). There were two documented episodes of recurrent ipsilateral pneumothorax (0.6%). Postoperative pulmonary function studies were done in 40 patients (unilateral, 29; bilateral, 11) 2 to 5 years after operation. The results indicate that there are no significant abnormalities compared with predicted values.**

Spontaneous pneumothorax has been recognized for a long time as a common cause of hospitalization in young people. Until the turn of the century, tuberculosis was considered responsible for the disease but it is now well substantiated [1, 4, 8, 17, 19, 20, 26, 33] that spontaneous rupture of nontuberculous subpleural blebs is the mechanism by which most spontaneous pneumothoraces occur.

The objectives of treatment are to obtain full reexpansion of the affected lung, to control the complications, and to prevent recurrences. In 1956, Gaensler [15] reported his experience with parietal pleurectomy for definitive treatment of recurrent spontaneous pneumothorax. This study is a review of our experience with apical pleurectomy done through an axillary incision and its long-term efficacy in preventing recurrence of the disease.

Material and Method

During the 16-year period 1962 to 1978, 362 patients had a total of 409 apical pleurectomies for problems related to spontaneous pneumothorax. Three hundred fifteen patients underwent unilateral pleurectomy and 47, bilateral. Excluded from this study were all the patients treated by total pleurectomy and a few who had talc poudrage.

The age distribution ranged from 11 to 67 years, with the majority (84%) of patients between 17 and 40 years old (Fig 1). Three hundred three pleurectomies were done on male patients and 106 on female patients, a 3:1 ratio.

Twenty-nine patients (8%) had known chest disease. Twenty had obstructive lung disease or asthma, and 7 had documented old tuberculosis; no patient in this group had active tuberculosis at the time of operation.

Surgical Indications

Seventy-three pleurectomies were done during the course of the first attack. Bilaterality was the indication in 23 patients but none of them was seen with simultaneous bilateral pneumothorax. Twenty-two patients had operation because of persistent air leak (beyond 10 days) and 10 because of failure to reexpand the lung despite adequate tube drainage. Other indications included hemopneumothorax (10 patients), a large bulla seen on a roentgenogram (6), and indications related to work (2).

Three hundred thirty-six pleurectomies were carried out because of recurrence (average, 2.5 pneumothoraces per patient). Most of these patients were not seen at the time of the first

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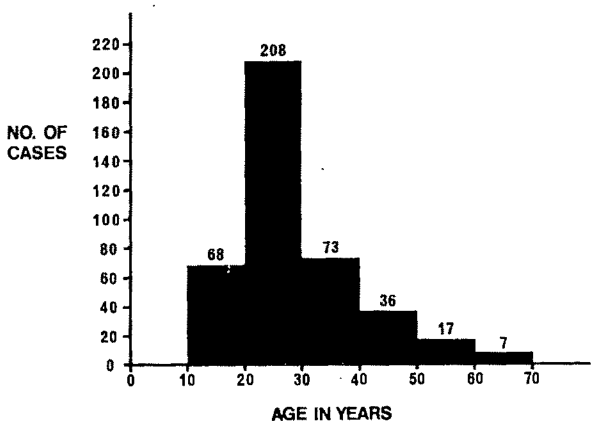

Fig 1. *Age in years.*

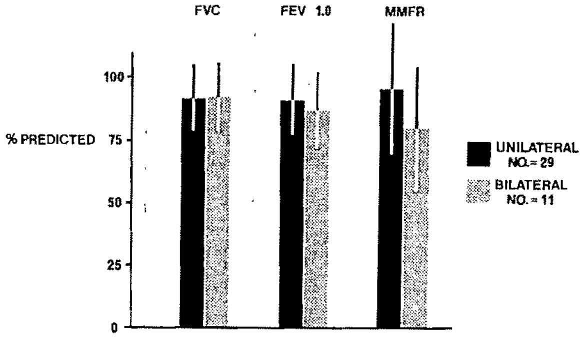

Fig 2. *Results of pulmonary function studies in 40 patients.* (FVC = *forced vital capacity;* FEV 1.0 = *forced expiratory volume after one second;* MMFR = *maximum midexpiratory flow rate.)*

pneumothorax but were referred for elective pleurectomy.

Operative Technique

The operation is performed with the patient in a 20-degree position on the operating table. The arm is elevated and fixed to the anesthetic screen crossbar. The surgical incision extends from the axilla along the external border of the pectoralis major. No muscles but the intercostal muscles are divided, and the chest cavity is entered through the third intercostal space.

Almost invariably, small vesicles can be identified at the apex of the lung and are excised with a stapling device; in some patients, however, there is only a scarred apex, which is excised or oversewn. The parietal pleura is then stripped from the endothoracic fascia starting at the incision and over the apex. Bleeding is meticulously controlled and a large tube left at the apex of the chest cavity. The operation is usually performed within thirty minutes.

Active mobilization of the arm is started the day after operation, and the chest tube is removed by the third postoperative day. The average hospital stay after operation is 6 days, and most patients return to active work four to six weeks after the operation. When bilateral pleurectomy is advisable, it is done in two stages a week to 10 days apart.

Results

There was 1 operative death related to an unsuspected brain tumor; the patient experienced acute cerebral hypertension and cardiac arrest. Two kinds of major complication were noted: hemorrhage and air leak necessitating reoperation. Three patients required reoperation for control of bleeding (1) or clot removal (2). Air leak was not a serious problem except in 1 patient who required completion of the pleurectomy 21 days after the initial operation.

Five minor types of complication were found: air-fluid level (18 patients), atelectasis, air leak for 5 to 15 days (9 patients), wound infection (3), and shoulder problem. Atelectasis was observed on roentgenograms in 14 patients but none required more than energetic chest physiotherapy for prompt expansion of the lung. Small air-fluid levels were common on the postoperative roentgenograms but they all disappeared spontaneously. Two patients needed prolonged physiotherapy for problems related to limited shoulder movement.

Three hundred ten patients (86% of all patients) have been followed from 1 to 16 years after operation (average, 4.5 years). There were two documented episodes of recurrent ipsilateral pneumothorax, both of which were treated conservatively. In most instances, there was no residual incisional pain and the cosmetic result was highly satisfactory.

Forty patients (unilateral pleurectomy, 29; bilateral, 11) had pulmonary function studies 2 to 5 years postoperatively (Fig 2). Since our center is regional and most patients live out of town, the selection was based on availability of the patient to come to the hospital for pulmonary function testing.

Vital capacity (VC) was above 85% of predicted value in 20 of the 29 patients who had unilateral pleurectomy and in 9 of the 11 patients who had bilateral pleurectomy. The difference between these two groups was not significant (χ^2 corrected: 0.173). There was also no significant difference between male (25) and female (15) patients.

Tabulated as percentage of predicted value, the VC was 91.6% ± 13.3, the forced expiratory volume after one second (FEV_1) was 90.0% ± 14.3, and the maximum midexpiratory flow rate was 91.4% ± 26.4. The FEV_1/VC also was normal at 82.0% ± 7.3. The comparison of these values between patients with unilateral and bilateral pleurectomies according to the *t* test of Student showed no significant difference.

Comment

Although spontaneous pneumothorax can be related to a wide variety of intrathoracic diseases, most reported series recognize a young, "apparently healthy" group of patients and an older group with generalized obstructive lung disease [1, 2, 22, 29, 30]. The young patients are usually tall, thin males [37], and the condition almost invariably consists of small, apical, subpleural vesicles [13, 22, 23]; sometimes, a scarred apex is the only recognizable lesion [22, 23, 30]. In the older group, diffuse emphysematous changes with or without bulla formation are the rule. The methods of treatment in complicated pneumothorax should take into account these characteristics of the underlying lung disease [6].

The great liability of pneumothoraces to recur constitutes a special problem since the chances of a further recurrence increase with the number of pneumothoraces [16, 24]. In order to control this complication, the goal at operation should be to remove the causative lesion [22] or obliterate the pleural space by the simplest possible technique.

Various methods of pleurodesis have been described and have been uniformly successful. Chemical pleuritis can be induced by closed or open intrapleural instillation of foreign substances [7, 8, 21, 25]. The main reported inconveniences are the toxicity [15] and the nonuniformity of pleural adhesions [10]. Talc has been shown to produce very intense fibrosis [14].

Mechanical irritation produced by scarification of the pleura is effective especially when combined with bulla excision [10, 11, 13, 20, 26, 27]. It is, however, technically difficult to do an adequate scarification through a small axillary incision because the hand cannot be inserted in the chest cavity; however, it is quite easy to remove the parietal pleura with surgical instruments.

Parietal pleurectomy creates an inflammatory surface with secondary adhesion of the lung to the endothoracic fascia. Gaensler [15] showed that parietal pleurectomy produces uniform adhesions between the pleura and the chest wall. He recommended this procedure for patients with diffuse lung disease and for those with no demonstrable lesion at the time of thoracotomy. Several authors have since described pleurectomy as the most secure procedure to obtain permanent pleurodesis [2, 4, 9, 18, 29, 31–33, 35].

Since the disease is nearly always located at the apex of the lung, we believe that in young people a limited apical pleurectomy combined with local excision of the diseased lung is sufficient for definitive control of the recurrences. The axillary approach has been described for pleural abrasion [11] and has been advocated for other intrathoracic procedures [3, 5]. It provides fast and good exposure while avoiding division of any respiratory muscle. The postoperative morbidity is minimal, the hospital stay is short, and the long-term cosmetic appearance of the scar is highly satisfactory. This last consideration is important in treating young patients. Most important, it prevents recurrences but does not disturb the pulmonary physiology even in patients with bilateral operations.

In this series, the mean VC of the whole group was normal, but 11 out of 40 patients had an absolute reading below 85% of the predicted value. Williams and Kane [36] in 1965 and DeTroyer and colleagues [12] in 1978 studied the pulmonary function of patients with previously documented pneumothorax who did not have operation. In the series of Williams and Kane, the mean VC was 87.5% of normal predicted values and 5 out of 15 patients had a VC below 85%, while in DeTroyer and colleagues' report the mean VC was 87.8% with 8 out of 21 patients below 85%. This research group demonstrated other physiological abnormalities in those patients: decrease in diffusing capacity, increase in residual volume, and decreased elastic recoil. These findings suggest that in a few patients there is some degree of asymptomatic emphysema. By comparison, our data show that there is no significant alteration in pulmonary function following pleurectomy. Only 11% of the patients (40 out of 362) were tested, but we believe that since this group was quite uniform (young, otherwise healthy), these 40 patients are representative of the whole population.

Several authors [10, 26] condemned pleurectomy because it abolishes the anatomical extrapleural plane, produces dense scarring, and makes further operation very difficult. Although we did not have to reoperate on such patients, we think that elective pleurectomy limited to the apex will make further thoracic operations more difficult but still perfectly feasible and safe. In summary, we believe that transaxillary apical pleurectomy should be recommended, especially in young people, for definitive treatment of recurrent spontaneous pneumothorax and for treatment of some complications related to the first attack.

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Discussion

DR. RICHARD A. RASMUSSEN (Grand Rapids, MI): Dr. Deslauriers and associates have presented a relatively large series of patients with recurrent spontaneous pneumothorax and some initial episodes treated by elective apical pleurectomy. Most of the patients were less than 40 years old and had few associated lung problems. The pleurectomy and appropriate excision of bullae were done through a limited axillary incision. This is a fairly aggressive approach. The more conservative technique of pleurodesis using dry gauze abrasion for both the pleural surfaces was not employed. The objectives of closing the site of air leak, excision of blebs, reexpansion of the lung, lasting pleural adherence with maximum preservation of function were accomplished satisfactorily. Pleurectomy, however limited, is attended by more bleeding than the less accepted procedures. Several of the patients in the series did require reoperation because of hemorrhage in spite of careful technique. This complication was emphasized in 1957 at a meeting of the American Association for Thoracic Surgery soon after pleurectomy was advocated for this condition. The procedure was discouraged and even condemned.

The surgical approach, though identified as "axillary," is perhaps really a modified anterior incision. It is through the third interspace and not like the true axillary incision used for first and second rib resections. I have used a similar anterior fourth interspace incision for the treatment of persistent pneumothorax and other lesions of the lung and thorax for many years. It permits good access and allows for anterior and posterior extension as needed. It does have the same danger of undue tension on the brachial plexus with subsequent shoulder dysfunction as mentioned by Dr. Deslauriers. Relaxation of the abducted arm during the opening and closing phase of the procedure would help avoid this complication.

Our experience with the treatment of persistent pneumothorax has been satisfactory using large-tube closed chest drainage for the first and second episodes. We have not hesitated to do a thoracotomy with excision of bullae combined usually with pleural abrasion. Occasionally, in instances of poor expansion, the pleura is freed but left in place. We have also tried to discourage the use of tobacco with its attendant cough, especially in this group of patients, a high percentage of whom are smokers and coughers.

DR. DAVID SKINNER (Chicago, IL): I greatly enjoyed Dr. Deslauriers's presentation and in spite of his difficulties, I think he made it clear that the operation of pleurectomy through a limited incision can be done with very low mortality and morbidity and with a very high success rate against which any other approach must be measured.

I bring to your attention a specific problem in the management of pneumothorax and the solution that has been devised to solve this in young women. As you probably know, the Playboy Club headquarters is in Chicago, and in 1975 we saw a former "Playmate of the Month" who made the centerfold by virtue of a rather large set of silicone implants in each chest. The patient was seen 14 days after a spontaneous pneumothorax with a residual pneumothorax and an air-fluid level in the right chest. A decortication pleurectomy was necessary. The problem was that the patient refused to have the implants removed or tampered with in the course of the operation. Eventually it was performed through a high hairline transaxillary incision. We achieved the desired results, and postoperatively the patient had a full reexpansion of the lung through a small incision made in the high axillary hairline.

Since then, knowing that this can be done and seeing as patients other women with silicone implants, we have routinely performed a transaxillary apical pleurectomy through an incision placed in the high axillary hairline. The results have been acceptable to the young women with this specific condition which complicates thoracic procedures.

DR. DAVID V. PECORA (Wilmington, DE): I enjoyed this presentation by Dr. Deslauriers and associates. No one can find fault with the results of this extensive series. It has always been difficult for me to understand why parietal pleurectomy should work at all. Perhaps operative trauma causes pleurodesis of surfaces not involved in the pleural stripping. Pleurectomy does occasionally result in severe hemorrhage, as we have seen.

I use a different approach. Through a small intercostal incision over the auscultatory triangle, large blebs usually are removed by twisting and tying them off. Both the parietal and the visceral pleura are then rubbed with sponges saturated in tincture of iodine. Patients recover full ventilatory function usually within six weeks.

DR. EDWARD A. GAENSLER (Boston, MA): Dr. Deslauriers must be congratulated on his excellent results. Also I thank him for acknowledging our initial publication. I appreciated his suggestion of a small axillary incision. We have always regretted the need for a formal posterolateral thoracotomy for an operation that involves only the very apex of the lung.

I have only two comments. The first concerns the need for parietal pleurectomy. We first performed this operation in a young airman when thoracoscopy revealed clusters of tiny blebs over the entire upper lobe—a condition that Sir Russell Brock [1] referred to as "cuckoo spit." Since then we have used parietal pleurectomy only in those rare cases of pneumothorax simplex in which involvement was too extensive for local wedge excision [2] and in cases of recurrent pneumothorax due to diffuse subpleural diseases, especially bullous periacinar emphysema [3] and lymphangioleiomyomatosis [4]. The late Dr. Shefts and his colleagues [5] showed that in more than 90% of apparently healthy young persons with pneumothorax simplex the cause was one or several tiny blebs at the very apex. More recently it has become apparent that this is the result of excessive tension due to gravity [6]. A tiny wedge excision is then curative, and the more complex parietal pleurectomy with its occasional complications is unnecessary. We have seen no recurrence after local wedge excision.

My second comment concerns the use of talcum poudrage. Talc not only causes a local granulomatosis but also, however pure, contains asbestos amphiboles. Ever since the relationship of asbestos to meosthelioma was demonstrated [7], we have warned against its use in operation since we anticipate the development of such tumors. Actually, the first case of mesothelioma due to poudrage with asbestos-related products has now been reported [8].

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DR. DOV WEISSBERG (Be'er Yaakov, Israel): In medicine as in politics, there are sometimes differences of opinion. Since the discovery of talc, I have never done pleurectomy for a spontaneous pneumothorax and I suspect I am not the only one in this audience. I insufflate talc, purified British Pharmacopoeia talc, free from asbestos and other contaminants. When blebs are present, I resect them through the axillary incision and then sprinkle talc lightly over the entire pleural surface.

However, in the majority of patients, without blebs, I insufflate talc at pleuroscopy, under vision. I use talc also for other indications, such as malignant pleural effusion and chylothorax, always using the same pleuroscopy technique. The hospital stay is only 3 to 4 days. In a small series of 77 patients, complete pleurodesis was achieved in 64 or 83% and partial pleurodesis, in 8 or 10.4%. There were only five failures, and no complications or deaths.

I compliment the authors on their presentation, but I disagree with them about the need for pleurectomy in patients with pneumothorax.

DR. DESLAURIERS: I thank the discussants for their comments. Over the past 50 years, several techniques have been described to control the problem of recurrent spontaneous pneumothorax, and most of them have been successful. Talc poudrage has been shown to produce effective pleural symphysis and is advocated by many; the disadvantages are the local toxicity, the nonuniformity of adhesions, and the possible carcinogenic effects with particular reference to mesothelioma. Pleural abrasion is effective but difficult to do through a small incision.

Because it is conceivable that new vesicles will form at a later stage, we think that for extra safety, parietal pleurectomy should be added to the local resection of the bullae. As Dr. Gaensler demonstrated in 1956, it provides an excellent way of producing pleural symphysis and when limited to the apex, it will not be a major problem should the patient need further operation in subsequent years.

The Management of Nonmalignant Intrathoracic Esophageal Perforations

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ABSTRACT **Eight patients with nonmalignant intrathoracic esophageal perforations recognized more than 48 hours (48 hours to 14 days) after rupture were treated at Toronto General Hospital between 1973 and 1978. Perforation was due to postemetic rupture in 7 patients and to instrumentation in 1. The patients were seen with pain (8), vomiting (7), fever (7), shock (4), respiratory insufficiency (5), pleural effusion (7), pulmonary infiltrates (7), and leukocytosis (6). All patients were managed with thoracotomy.**

Direct suture closure of the perforation was carried out in 4 patients with midesophageal perforations. Postoperative localized leaks developed in 2 of these patients but healed with conservative management. Cervical esophagostomy and esophageal diversion were used in 1 patient in whom a severe empyema developed in the postoperative period. Direct suture closure, reinforced with a gastric patch, was used to close three lower esophageal perforations. None of these patients had a postoperative leak but all developed subsequent reflux esophagitis. All 8 patients survived.

In patients with delayed recognition of a nonmalignant intrathoracic esophageal perforation, elimination of continued chemical and bacterial contamination can be achieved by a clear definition and closure of the esophageal mucosal margins. The obliteration of potential pleural spaces by good tube drainage, lung decortication, and the elective use of mechanical ventilation with positive end-expiratory pressure decreases the incidence of uncontrolled intrapleural sepsis.

Perforation of the intrathoracic esophagus is a life-threatening condition and requires prompt diagnosis and immediate surgical management. When a perforation of the intrathoracic esophagus is untreated, gastric juices and bacteria-laden oropharyngeal secretions leak into the mediastinum and produce a fulminant inflammatory response. At first, the mediastinitis is chemical but within hours of the rupture, bacterial invasion occurs. If the rupture extends into the pleural space, the mediastinitis may be less severe but the pleural cavity becomes extensively infected. In either case, dehydration, bacteremia, and circulatory collapse usually develop within hours.

Factors affecting the outcome of esophageal ruptures include the age and general health of the patient, the location, size, and cause of the perforation, the interval between rupture and treatment, the type of treatment, and the presence of preexisting esophageal disease. After 40 years of age, mortality from spontaneous rupture of the esophagus increases progressively with age [12]. Blichert-Toft [2], reporting results between 1944 and 1969, found that patients who had operations within 12 hours had a mortality of 22% and within the next 12 hours, 36%. However, if treatment was delayed beyond 24 hours, the mortality rose to 64%. Primary repair produced a 34% mortality while nonoperative treatment resulted in an 80% rate of mortality.

Although it is agreed in general that management of the recently ruptured thoracic esophagus is direct suture with drainage of the pleural space, there is disagreement as to the best method of managing late intrathoracic esophageal perforations [4, 5, 8–10, 13–15]. Most authors concur that tube drainage of the mediastinum and pleural cavity, administration of antibiotics, and adequate nutrition are important components of treatment of esophageal perforations with delayed recognition. However, there is a divergence of opinion con-

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cerning direct suture closure of the perforation [3] and the use of esophageal patches [4, 5, 9, 11, 13, 14], esophageal resections [7], and esophageal exclusion and diversion [6, 8, 15].

This report describes the recent experience at the Toronto General Hospital with 8 consecutive patients who had nonmalignant intrathoracic esophageal perforations with late recognition. They were treated, when possible, by direct closure of the esophageal mucosa and obliteration of potential pleural spaces by good tube drainage, lung decortication, and the elective use of mechanical ventilation with positive end-expiratory pressure (PEEP) to maintain lung expansion.

Materials and Methods

The hospital records of all patients with a diagnosis of perforation of the intrathoracic esophagus treated at the Toronto General Hospital during the past six years (1973 through 1978) were reviewed. There were 15 patients in whom this diagnosis was established. In the 8 patients analyzed here, the perforations were recognized more than 48 hours (48 hours to 14 days) after rupture. This group consisted of 3 women and 5 men ranging from 34 to 80 years old.

Instrumentation accounted for one perforation and postemetic rupture for seven perforations. Five of the 8 patients had an esophageal stricture, 4 as a result of reflux esophagitis and 1 as a result of a lye burn.

The patients were seen initially with pain (8 patients), vomiting (7), fever (7), hypotension (4), hypoxemia (5), pleural effusion (7), pulmonary infiltrates (7), and leukocytosis (6). Two patients required preoperative mechanical ventilation. A preoperative diagnosis of esophageal perforation was made in 7 of the 8 patients by esophagogram (6 patients), esophagoscopy (5), and in some patients by both methods. Four of the eight perforations occurred in the midesophagus with, the rest in the lower esophagus. All midesophageal ruptures were associated with distal esophageal strictures.

All patients had a thoracotomy. The mucosa was closed in 7 patients and reinforced with a gastric patch in 3. The pleural space was drained in all patients. Pulmonary decortication was performed in 2 patients to fully reexpand the lung and obliterate the pleural space. Elective postoperative mechanical ventilation with PEEP was used in 4 patients.

Direct Suture of the Perforation

Four patients with spontaneous midesophageal ruptures underwent a right thoracotomy and direct suture closure of the perforation. The margins of the mucosa were defined, debrided, and accurately closed.

Patient 1

A 69-year-old woman was admitted with a 2-day history of vomiting and retrosternal chest pain, which radiated into the back. She was febrile but normotensive. A contrast esophagogram revealed a small posterior wall perforation at the junction of the lower and middle thirds of the esophagus plus a distal esophageal stricture. Esophagoscopy revealed the perforation as well as a benign esophageal stricture.

At thoracotomy, a 2 cm perforation was visualized 7 cm below the azygos vein. The esophagus was dilated with a No. 50 Maloney bougie. The mucosa around the perforation was debrided and closed with interrupted 4-0 chromic catgut sutures. The muscle was closed with interrupted 3-0 chromic catgut sutures. The pleural space was cleansed and drained with one chest tube. No complications occurred in the postoperative period. The patient was discharged 15 days after the operation and could eat a normal diet. She has no esophageal symptoms at present.

Patient 2

A 68-year-old man who had epigastric pain, fever, and a right pneumothorax was admitted 6 days after a bout of severe vomiting. A right chest tube drained 2 liters of purulent fluid. A contrast esophagogram revealed a large, midesophageal perforation.

After resuscitation, the patient underwent a right thoracotomy. A 4 cm tear in the esophagus was located 10 cm proximal to the gastroesophageal junction. The defect in the muscle layer was surgically extended longitudinally at each end of the perforation in order to visualize the mucosa. The esophagus was closed in two layers and wrapped with pleura. The pleural cavity was decorticated, cleansed, and drained with two chest tubes.

A leak from the suture line developed and persisted for two weeks. An esophagoscopy done at that time showed that a chest tube had eroded through the suture line into the esophageal lumen. The chest tube was shortened and since there was no distal esophageal obstruction, the fistula closed in a week. The patient required esophageal dilation for dysphagia on one occasion after the operation. At present, he has no esophageal symptoms.

Patient 3

An 80-year-old woman with a history of esophageal obstruction secondary to achalasia was admitted to the hospital with a 3-day history of food impaction and recurrent vomiting. Two pieces of meat were removed by endoscopy and a right posterolateral esophageal perforation could be visualized 30 cm from the teeth. The perforation into a mediastinal abscess cavity was confirmed by contrast esophagogram.

After the patient was resuscitated, a large mediastinal abscess was visualized through a right thoracotomy. The abscess cavity was opened and traced to a 2 cm tear in the esophagus just below the azygos vein. The perforation was debrided and closed with interrupted 2-0 chromic catgut sutures. A long myotomy was carried out distally from the perforation to the gastroesophageal junction. The abscess cavity was debrided and drained with two chest tubes. A gastrostomy tube was brought out through a stab wound in the abdominal wall. There was no leak from the esophageal suture line. The patient was discharged from the hospital and could eat a solid diet; she had no dysphagia.

Patient 4

A 79-year-old man with a history of reflux esophagitis was admitted with a 4-day history of vomiting and upper abdominal pain. He was hypotensive and dyspneic and had a right pleural effusion. A tube placed in the right chest drained 2 liters of purulent material. A contrast esophagogram showed a midesophageal perforation draining into the right chest. Esophagoscopy revealed gastric-lined mucosa below the perforation but no evidence of an esophageal stricture.

After resuscitation, the patient underwent a right thoracotomy. A 3 cm tear in the esophagus was visualized 4 cm below the azygos vein. The esophagus was mobilized, and the defect in the muscle layer was surgically extended at either end to ensure adequate exposure of the mucosal margins. The mucosa was debrided and was closed with interrupted 3-0 chromic catgut sutures. The muscle was then approximated with interrupted 3-0 silk sutures. The pleural cavity was decorticated and drained with two chest tubes. The patient was placed on elective mechanical ventilation with PEEP for 2 days.

Eight days after the operation, a small, asymptomatic leak at the suture line was documented radiographically. It had closed by 14 days after the operation. The patient was discharged 20 days after the operation. Esophageal dilation was carried out for dysphagia one month after the operation. The patient has no dysphagia at present, and the reflux esophagitis is being treated conservatively.

COMMENT. The esophageal suture line leaked in 2 out of these 4 patients. The leaks were well controlled, and the patients showed no evidence of sepsis. In Patient 2, the chest tube eroded into the esophagus since it was placed too close to the suture line. Dilation of the distal esophageal stricture and simple suture closure of the perforation resulted in a low incidence of postoperative esophageal symptoms in these patients.

Exclusion and Diversion of the Esophagus

Patient 5

A 53-year-old woman with a lye stricture of the esophagus was admitted 2 days after undergoing esophagoscopy for removal of a food bolus stuck at the lower end of the esophagus. On admission she was dyspneic and febrile, and she had cervical crepitus and a large right pleural effusion. A right chest tube drained 1,200 ml of purulent fluid. A contrast esophagogram showed a large perforation into the right chest just above the gastroesophageal junction.

After resuscitation, the patient underwent an esophagoscopy, which revealed a midesophageal stricture as well as a stricture just distal to the esophageal rupture. An 8 cm perforation was visualized at the lower end of the esophagus through a right thoracotomy. Since there was not sufficient esophageal tissue left to close the perforation, the proximal and distal esophagus were oversewn. The pleural cavity was debrided, cleansed, and drained. The esophagus was decompressed with a cervical esophagostomy and gastrostomy.

In the postoperative period, the patient remained febrile and required a Clagett procedure for drainage of a right empyema. Thirty-five days after the operation, she was discharged home but had to have gastrostomy tube feedings. A left colon interposition was done three months after the esophageal perforation. As a result of the complications from the colon interposition, the patient required tube feedings for ten months after the initial operation.

COMMENT. Although this operation may be necessary in poor-risk patients with large perforations, the magnitude of the operation and the duration of postoperative morbidity do not warrant its use in most patients with esophageal perforations.

Direct Suture Reinforced with Gastric Patch

Three patients with distal esophageal perforations had direct closure of the perforation and reinforcement with a partial [2] or complete wraparound of stomach.

Patient 6

A 65-year-old man was admitted 3 days after undergoing a laparotomy for epigastric pain and vomiting. There were no abnormalities at the time of laparotomy. The patient's condition gradually deteriorated; respiratory failure, bilateral serous pleural effusions, renal failure, and hypotension developed, and he became obtunded. Fourteen days after laparotomy, material like coffee grounds was noted to be draining from the right chest tube and a contrast esophagogram showed a gross leak from the gastroesophageal junction into the left chest.

After resuscitation, the patient underwent a left thoracotomy. The gastroesophageal junction was mobilized, and the muscle at each end of the perforation was extended longitudinally. The mucosa was debrided and closed with interrupted 3-0 chromic catgut sutures. The muscle was closed with interrupted 3-0 silk sutures. The perforation, which was approximately 2 cm from the gastroesophageal junction, was then partially wrapped with the piece of stomach brought up through the hiatus. A gastrostomy tube was left in place.

The patient's postoperative course was complicated with episodes of atrial fibrillation, acute tubular necrosis, grand mal seizures, and a staphylococcal septicemia. However, he gradually improved and received nutritional support by gastrostomy feedings. The atrial fibrillation and seizures were controlled. His serum creatinine stabilized to 2 mg per 100 ml, and he was able to maintain a normal fluid and electrolyte balance. A contrast esophagogram done 11 days after the operation revealed no leak from the lower end of the esophagus. Twenty-one days after thoracotomy, a small bowel obstruction developed and required a laparotomy for lysis of adhesions. The patient recovered from this operation without any difficulty and was discharged home six weeks after admission. Symptoms of severe reflux esophagitis developed, which had not been present preoperatively. The patient required strict medical management with antacids, elevation of the head of his bed, and frequent small meals. He also required intermittent bougienage for dysphagia.

Patient 7

A 66-year-old man was admitted with a 3-day history of retrosternal and epigastric pain. The pain started during an episode of vomiting, 6 hours after a suprapubic prostatectomy. The patient had also undergone an abdominal hiatus hernia repair for ulcerative esophagitis five years prior to this admission. On admission, he was hypotensive and dyspneic, and he had bilateral pleural effusions. Bilateral chest tubes drained purulent fluid. A contrast esophagogram revealed a perforation 2 cm above the diaphragmatic hiatus.

After the patient was resuscitated, the stomach was mobilized and wrapped 360 degrees around the site of the perforation in the chest. The pleural cavity was decorticated, cleansed, and drained with two chest tubes. The patient required mechanical ventilation for 4 days after the operation. There was no leak from the suture line in the postoperative period. The patient was discharged 30 days after the operation. He could take a normal diet but experienced occasional dysphagia after eating dry bread.

Three years after the repair of the esophageal perforation, reflux esophagitis and a bleeding gastric ulcer in the fundoplication developed. The gastric ulcer was oversewn, and a transthoracic gastroplasty and hiatus hernia repair were done. In the postoperative period, a recurrent gastric hemorrhage developed and required a total gastrectomy and Roux-en-Y repair. There was a leak from the upper anastomosis, and a left empyema developed. The patient died in septic shock two weeks after the last operation.

Patient 8

A 34-year-old man was admitted with a 2-day history of epigastric pain following a bout of vomiting. On admission he was dyspneic and febrile and had a left pleural effusion. A left chest tube drained 1 liter of bile-stained fluid. A contrast esophagogram revealed a perforation 3 cm above the gastroesophageal junction.

Through a left thoracotomy, the esophageal perforation was debrided and closed in two layers. The stomach was mobilized and partially wrapped around the perforation in the chest. The patient received elective mechanical ventilation for 48 hours. There were no leaks from the esophageal suture line in the postoperative period. The patient required a gastroplasty and hiatus hernia repair for severe reflux esophagitis eighteen months after the operation.

COMMENT. Although the use of intrathoracic gastric patches to reinforce the esophageal suture line prevented esophageal leakage in this study, the enlargement of the hiatus, the intrathoracic positioning of the stomach, and the failure to do a standard antireflux operation resulted in a high incidence of reflux esophagitis.

Comment

Despite awareness of the seriousness of intrathoracic esophageal ruptures, delay in diagnosis is the major stumbling block to lowering morbidity and mortality. In this study, 6 of the 8 patients saw their primary physician within 24 hours of experiencing symptoms of esophageal rupture. Initial diagnoses included myocardial infarction, pulmonary embolus, spontaneous pneumothorax, and perforated duodenal ulcer. Rupture of the esophagus should always be considered in patients with severe chest or upper abdominal pain and signs of infection.

Early in the course of an esophageal perforation, the diagnosis may only be suspected from a characteristic history. However, once mediastinitis becomes established, chest or abdominal pain, dyspnea, fever, hydropneumothorax, or mediastinal emphysema are highly suggestive of an esophageal rupture. These symptoms and signs demand that a Hypaque (diatrizoate meglumine) swallow be performed. Esophagoscopy helps confirm the location of the perforation and establish the caliber of the distal esophagus.

Patients who are seen late after esophageal rupture are dyspneic, dehydrated, and very often hypotensive. After fluid resuscitation, antibiotics, and tube drainage of the infected pleural spaces, the patient's condition improves and there is reluctance to repair the esophageal rupture by operation. However, if an operation is not done, soilage of the mediastinum and pleural cavity progresses to severe empyema and the patient dies of the complications of uncontrolled sepsis. The well-documented high mortality associated with nonoperative management of old esophageal ruptures has led to more aggressive surgical management in most centers [2].

As time goes by after the rupture, the esophageal muscle around the perforation becomes inflamed and necrotic. The inability of this tissue to hold sutures was recognized in the past, and recurrent leakage often has been reported with direct suture closure of old esophageal tears. Consequently, complex procedures have been designed for the management of patients with esophageal perforations.

Use of Silastic T-tubes or the Celestin tube [1] to exteriorize or put a stent on the perforation has met with favorable results in selected patients. Resection of the rupture and esophagogastrostomy may be indicated for perforated neoplasms [7]. However, the risk of such an extensive operation, if not done for cancer, is prohibitive. Johnson and co-workers [6] recommended complete exclusion of the esophageal perforation by suture closure of the esophagus at the cardia and cervical esophagostomy with closure of the distal end. This technique was modified by Menguy [8] and later Urschel and colleagues [15] who placed a tape around the cardia to prevent reflux and performed a loop cervical esophagostomy to divert the oropharyngeal secretions. These techniques may be useful for very large esophageal perforations that cannot be closed directly. The 1 patient in this study who was treated by this technique required a rib resection and drainage for uncontrolled intrapleural sepsis. She underwent a left colon interposition three months after the operation but required gastrostomy feedings for ten months after the rupture.

In patients with delayed recognition of nonmalignant intrathoracic esophageal perforation, elimination of continued chemical and bacterial contamination can be achieved by primary closure of the esophageal perforation. Although the esophageal muscle is often inflamed and necrotic, the mucosa usually remains viable and can hold sutures securely. The mucosal tear is often longer than the muscle tear so it is important to mobilize the esophagus and to extend the muscle tear at each end of the perforation in order to define, debride, and close the mucosa accurately with interrupted sutures. The inner aspect of the esophagus should be carefully inspected before closure of the rupture in order to rule out the presence of cancer, stricture, or another tear. The muscle layer should be debrided and closed with interrupted sutures.

Various tissues have been used to reinforce the esophageal suture line and thereby avoid leaks. Thal and Hatafuku [14] used the gastric fundus to reinforce the closure or to bridge the defect in the esophagus. Although the gastric patch successfully prevented esophageal leakage in 3 patients in this study, neither partial nor complete gastric wraparound of the intrathoracic esophagus prevented gastric reflux. In these patients, enlargement of the hiatus, intrathoracic positioning of the cardia, and inability to do a standard antireflux procedure may have contributed to the reflux. Two of the 3 patients required a subsequent antireflux operation for severe esophagitis. Pericardial [9] and diaphragmatic tissue [13] also have been used. The benefits of operations using these tissues are offset by the inevitable contamination of the pericardial and peritoneal cavities. The drawbacks of the preceding techniques make the use of thickened parietal pleura [5], lung [11], or intercostal muscle [4] for support of the esophageal suture line the most appealing techniques since healthy local tissue is used without added risk to the patient.

Potential intrapleural dead space is eliminated by adequate pleural drainage, pulmonary decortication, and the elective use of mechanical ventilation with PEEP in order to maintain full expansion of the lung. Finally, the use of total parenteral nutrition for maintenance of the protein and caloric needs of these catabolic patients is mandatory for increased survival [10].

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Discussion

DR. P. RICHARD CARTER (West Covina, CA): I compliment Dr. Finley and his distinguished colleagues for an excellent presentation—a reappraisal of primary closure for delayed, nonmalignant esophageal perforation. The most important factor contributing to the continuing high mortality of this devastating lesion is failure to make an early diagnosis. If recognition is prompt, successful treatment can be carried out. It consists of intensive supportive measures, direct transthoracic repair by primary suture, and adequate drainage of the mediastinal and pleural spaces.

When recognition is delayed, however, perforating esophageal wounds produce a fulminant mediastinitis, which severely damages the esophagus and often makes it either unsuturable or precariously reparable. Suture line leakage with recurrent perforation often follows, resulting in prolonged morbidity or death of the patient.

Not only does delay in diagnosis markedly increase the death rate, but direct operative repair is much more likely to be successful if done as soon as possible after injury. Thus, greater emphasis on earlier diagnostic studies is important in a catastrophic situation in which survival is directly related to prompt surgical intervention. Any patient with an unexplained pleural effusion should have an esophagogram, but a negative study by no means excludes the possibility of esophageal rupture. Direct endoscopic visualization of the perforation should then be done, as was used by the Toronto group. In addition, endoscopic stricture dilation under fluoroscopy, combined with a simultaneous contrast esophagogram, facilitates immediate recognition of instrumental perforation.

Multiple, more complex techniques—many authored by members of this Society—are usually necessary after delayed diagnosis. Buttressing a precarious primary closure is advisable, and coexisting distal obstruction, if present, must be corrected. Many techniques of reinforced patch closures are advocated, but the use of parietal pleura or gastric wraparound is especially helpful.

Although based on a small but well-managed series of patients, this study suggests that delayed esophageal perforation may be closed primarily in selected patients, when reinforced by patching techniques. The key to proper surgical treatment is the condition of the esophagus at the time of operation.

In closing, I ask the authors to define their indications for esophageal exclusion and diversion, and to comment on their use of PEEP in these patients.

DR. J. B. SHAMMASH (Springfield, MA): I endorse early operative management of benign perforations, preferably by primary suture, even when diagnosis may be delayed a number of days. Two patients were treated in this manner. One was seen 65 hours after perforation and the other, 10 days after perforation when the thoracostomy tube, inserted to drain an empyema, did not control his septic course. The perforation in the distal esophagus led to a large collection in the mediastinum, which poured out through a small opening in the mediastinal pleura to form a right-sided empyema. A 3 cm oval perforation was closed, the mediastinum widely drained, and the pleura decorticated. The patient did well.

A more rare and less understood type of limited tear deserves mention—the so-called spontaneous intramural hematoma, which does well without operative intervention. A 65-year-old woman noted sudden substernal pain radiating to the interscapular area associated with hematemesis after she ate a piece of toast. She had no previous dysphagia, and she was not on a regimen of anticoagulants. Chest roentgenogram on admission was normal. A few hours later, bilateral pleural effusions developed. A barium swallow revealed extravasation of barium intramurally throughout the length of the thoracic esophagus, markedly narrowing the lumen. Esophagoscopy showed submucosal hemorrhage obstructing the lumen. Serous fluid, which was positive for salivary amylase, drained from a left thoracostomy. The patient did well on conservative management and was drinking in a week. Of particular note, there was a lack of "systemic" or marked febrile response that is usually seen with frank mediastinal-pleural perforation of the esophagus.

Dr. Finley, have you encountered similar cases of this entity? If so, how were they handled?

DR. ANTHONY S. PATTON (Peabody, MA): Thank you very much for the opportunity to discuss this most interesting paper. I think it is a very important subject to most of us in thoracic surgery.

We reviewed our experience from Salem Hospital at a meeting in New England in 1978. At that time, we had seen 14 patients with spontaneous perforations of the esophagus, and since then have added 4. Nine of these eighteen perforations were the very late variety discussed by Dr. Finley. The main point of our presentation was that these patients often are not seen with the typical Boerhaave's syndrome but often have most peculiar symptoms, usually in association with other gastrointestinal diseases. We had patients who were seen with unusual problems, such as pericardial tamponade, due to an unrecognized spontaneous esophageal perforation that had occurred up to a month earlier. I emphasize that esophageal perforation must be considered in the diagnosis of unusual thoracic problems.

I take minor issue with Dr. Finley's group for negating, I think, the concept of esophageal exclusion. We have found this concept to be a good one. I do not mean that we do tapings or primary resections for benign lesions, as some authors have suggested, but we do simple drainage from above with large Levine tubes and from below with a gastrostomy. A jejunostomy for feeding is usually added. A primary attack on the lesion, if it is feasible, is also done, and extensive mediastinal drainage is carried out. We have found this method of esophageal exclusion very successful and have had few mortalities and troubles when these steps are used with vigor.

DR. HERMES C. GRILLO (Boston, MA): The principal point of contention in handling perforations recognized late has been whether or not to exclude the esophagus, because of the problem of releakage. I want to update the report that Dr. Wilkins and I [1] made a few years ago about using one of the several tissue patches, a pedicled pleural flap, to avoid this problem. Everyone seems to agree on the other principles—decortication, expansion of lungs, drainage, and elimination of distal obstruction. We now have treated 9 of these patients. All have done well, except for the last 1 who had a pseudodiverticulum, which healed spontaneously. In patients with perforations, the pleura is very thickened due to inflammation. It is easily accessible either for flap coverage or circumferential wrapping.

I agree with the argument of Dr. Finley that anatomical exclusion is unnecessary.

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DR. PETER C. PAIROLERO (Rochester MN): I, too, congratulate the authors for their excellent presentation. We at the Mayo Clinic are in agreement with many of the points that they have stressed. However, in addition to the elimination of both bacterial and chemical contamination, an additional goal of treatment must be to eliminate any distal esophageal obstruction. This is especially true in those patients with instrumental perforations secondary to stricture.

As already stated, the ideal treatment time is immediately after perforation before sepsis has developed. However, once the perforation becomes chronic and the patient has survived the hazards of septic shock, treatment at this late stage also has a good chance of success.

We recently reviewed our series of 11 patients with spontaneous rupture of the esophagus seen during the past ten years. Two patients were treated early, that is, less than 24 hours after perforation. Both were treated with thoracotomy, esophageal closure, and pleural drainage, and both survived. An additional 5 patients were treated later than 5 days following perforation, and 4 survived. Two of these patients were treated by thoracotomy, closure, and drainage; 2 patients by chest drainage only; and 1 by esophageal exclusion. The single death in this group occurred in 1 of the patients treated by chest drainage only. On the other hand, of the 4 patients treated in the intermediate period, that is, between 1 to 3 days following perforation, only 1 patient survived. Three of these patients were treated by thoracotomy, closure, and drainage, with 1 survivor, and 1 by esophageal exclusion. Thus, it may be not so much what we do but rather the timing of the operation that is all important, provided the goals of treatment are met. Dr. Finley, what were your results in those patients in this intermediate zone? Also, what are your recommendations if thoracotomy, closure, and drainage fail?

DR. KAMAL A. MANSOUR (Atlanta, GA): I compliment the authors for their magnificent results. However, since their patients survived the acute episode of rupture, I wonder how many would have made it without any surgical intervention.

In our series of 47 patients with spontaneous rupture of the esophagus reported some years ago, 3 survivors were seen by us initially for management of residual complications late in their disease. Two patients had leakage into the subphrenic space and 1 was seen with an esophagopleural cutaneous fistula some six months after the onset of the acute episode.

This paper supports the fact that primary repair is the treatment of choice whenever possible. However, it does not exclude other modalities of treatment such as T-tube drainage, esophageal exclusion, and even esophageal resection in late cases of esophageal rupture. What about patients with stricture of the esophagus distal to the perforation? We have seen 7 such patients. And how about patients with massive inflammation and necrosis of the esophageal wall, or patients with severe malnutrition and alcoholism in whom healing capacity is very poor? We agree with the authors on the importance of postoperative mechanical ventilation to minimize pleural dead space and overcome ventilatory deficiency.

I have one question for the authors. How would you explain the high incidence of postoperative dysphagia—6 out of your 8 patients?

DR. LYMAN A. BREWER, III (Loma Linda, CA): The Egyptians described an esophageal wound in the Smith Papyrus, 3000–2500 BC. One case titled "Instruction concerning a wound of the throat" states: "If thou examines a man having a gaping in his throat, piercing through his gullet; if he drinks water he chokes, it comes out of the mouth of the wound; it is greatly inflamed so that he develops fever from it, thou should draw together that wound with stitching." This is the first recorded use of sutures.

In World War II, 4,444 years later, we began to repair esophageal wounds; no repairs were reported in World War I. In 1944, a casualty with a wound of the esophagus and empyema 7 days after wounding showed esophageal contrast medium entering the pleural cavity. After esophagus repair and pulmonary decortication, the right lung completely expanded. Pulmonary decortication was revived in World War II by Drs. Burford, Samson, and myself. We successfully treated 3 other patients with esophageal wounds with delayed suture. This technique, first used by the ancient Egyptians 3000–2500 BC, was modernized and reported in volume two of *Surgery in World War II, Thoracic Surgery* (pp 269–297) by Dr. Burford and myself.

DR. FINLEY: I thank all the discussants for their comments. I'm sorry that I missed Dr. Brewer's first reference in my literature search.

A number of good points have been raised concerning this very controversial subject, and I will talk first about esophageal diversion. In most instances we try to close the esophageal wall where possible unless we are going to completely obstruct the esophagus. We try to divert or decompress the esophagus by using a sump nasogastric tube above and a gastrostomy tube below the perforation. This technique appears to protect against mediastinal contamination as well as cervical esophagostomy and ligation of the gastroesophageal junction.

Most of our patients were diagnosed 2 to 5 days after perforation but a few were seen late and did very well. We used the pleural patch, as described by Dr. Grillo, with success.

Six of our 8 patients had postoperative dysphagia. Four improved with dilation early in the postoperative period. Two patients had prolonged dysphagia. One had stenosis at the esophagocolonic anastomosis, and the second had a column-lined esophagus with recurrent peptic stricture of the esophagus.

Tumor-Simulating Thoracic Extramedullary Hematopoiesis

Hans Elbers, M.D., Jan v.d. Stadt, M.D.,
and Sjoerd Sc. Wagenaar, M.D.

ABSTRACT **Two patients with massive, tumor-simulating extramedullary hematopoiesis are presented. In 1 patient with homozygous β-thalassemia, a progressive paraparesis developed because of a mass of ectopic marrow in the spinal epidural space. Surgical removal and radiotherapy were successful. The second patient, who died during surgical biopsy, had posterior mediastinal masses without any apparent cause. A correct preoperative diagnosis may avoid unnecessary surgical intervention. It is suggested that heterotopic marrow should be included in the differential diagnosis of a mass in the lower thoracic region.**

Extramedullary hematopoiesis is found in adults as a compensatory response to either chronic hemolytic conditions or bone marrow replacement. Heterotopic marrow usually is microscopic and most frequently involves the liver, spleen, and lymph nodes. However, on rare occasions the extramedullary marrow takes the form of tumor-like masses [6, 8, 13]. The occurrence of masses of extramedullary hematopoiesis without apparent cause is very uncommon [7]. This report presents the clinical aspects and pathological findings in 2 patients with tumor-simulating marrow heterotopia.

Patient 1

A 27-year-old man of Chinese-Negro ancestry was admitted to the hospital because of progressive paraparesis. The symptoms had started in the left leg. For some years he was known to have anemia and splenic enlargement due to homozygous β-thalassemia.

On physical examination, the spleen was palpable 10 cm below the left costal margin, pulse rate was 76 beats per minute, and blood pressure was 130 mm Hg systolic and 90 mm Hg diastolic. The patient had paresis of both lower limbs. Abdominal reflexes were absent, and tendon reflexes of both lower limbs were exaggerated. Plantar responses were indifferent. The sensation of pain was impaired below the sixth thoracic segment, with hypoesthesia and reduced vibration sense.

The hemoglobin was 5.2 mmole per liter and the white cell count, 7×10^9 per liter. The osmotic fragility of the erythrocytes was increased. The hemoglobin value found by the alkaline denaturation technique was 75%. Cellulose acetate electrophoresis disclosed a pattern of predominantly hemoglobin F, and there was an increased percentage (6.7%) of hemoglobin A_2. Roentgenograms showed a coarsened trabecular pattern of the vertebral bodies. Myelography revealed a complete block at the fifth thoracic vertebra (Fig 1).

Laminectomy was performed, and a highly vascular extradural mass extending from the fifth to the eighth thoracic vertebra was found. Complete removal of the mass was effected macroscopically and was followed by postoperative radiation therapy (2,800 rads). Microscopic examination of the vascular mass showed active hematopoietic tissue with numerous precursors of the red cell series, scattered megakaryocytes, and occasional myeloid cells.

At one year after laminectomy, the patient has made a dramatic recovery. Leg motion and

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We thank Prof. Dr. F. L. M. Peeters, Department of Roentgenology, Wilhelmina Gasthuis, University of Amsterdam, Amsterdam, for providing the roentgenological information concerning the first patient. We also owe a debt of gratitude to Prof. Dr. G. Bras, Institute of Pathology, State University of Utrecht, Utrecht, for his critical review of this article.

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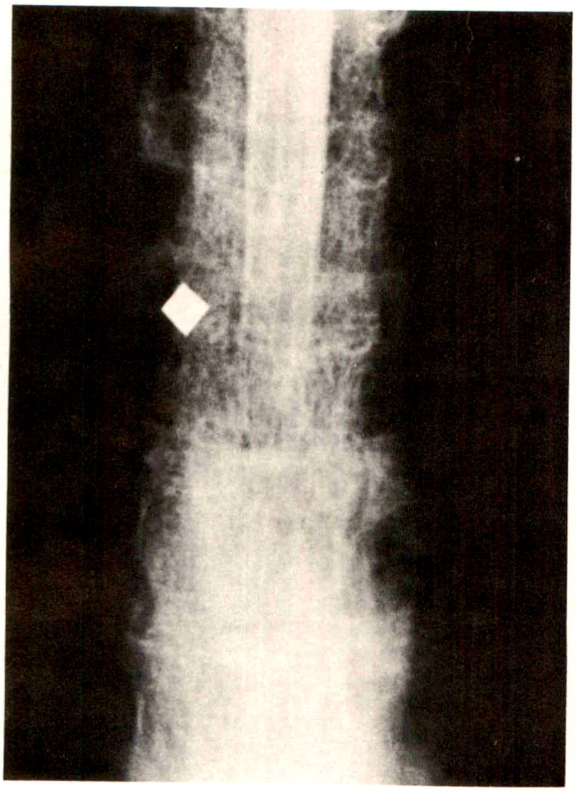

Fig 1. Myelogram showing a complete block at the fifth thoracic vertebra caused by extramedullary compression.

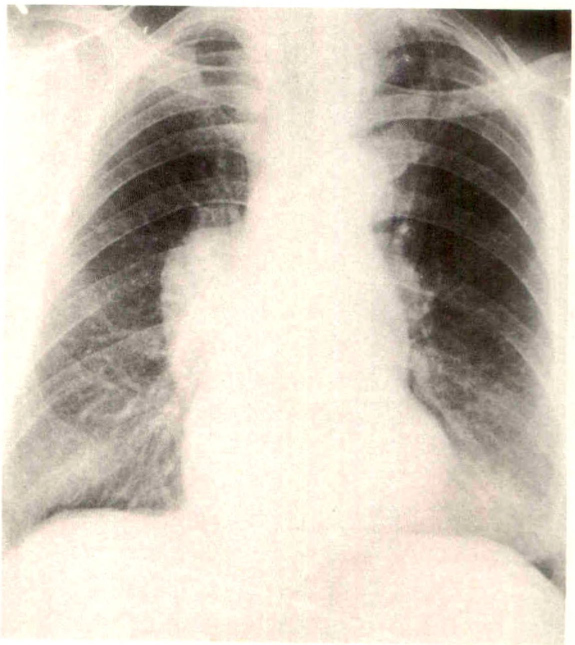

Fig 2. Chest roentgenogram showing a well-circumscribed, homozygous mass projecting into the hilus of the right lung.

the power of the lower limbs are normal, although slight hypoesthesia and hypalgesia remain.

Patient 2

An 81-year-old man was admitted to a hospital elsewhere for a checkup for diabetes mellitus. Roentgenograms of the chest showed a circumscribed density projecting into the apex of the lower lobe of the right lung (Figs 2, 3). The past history included cholecystectomy and a transurethral prostatectomy because of hyperplasia. He had no complaints and was apparently in good health. The temperature was 37.8°C, pulse rate was 80 beats per minute, and blood pressure was 165/85 mm Hg. Physical examination revealed no abnormal findings.

Laboratory studies disclosed the following values: hemoglobin, 10 mmole per liter; hematocrit, 42%; leukocyte count, 15.4 × 10^9 per liter (normal differential count). The erythrocytes were normocytic and normochromic. Blood chemistry data all fell within nor-

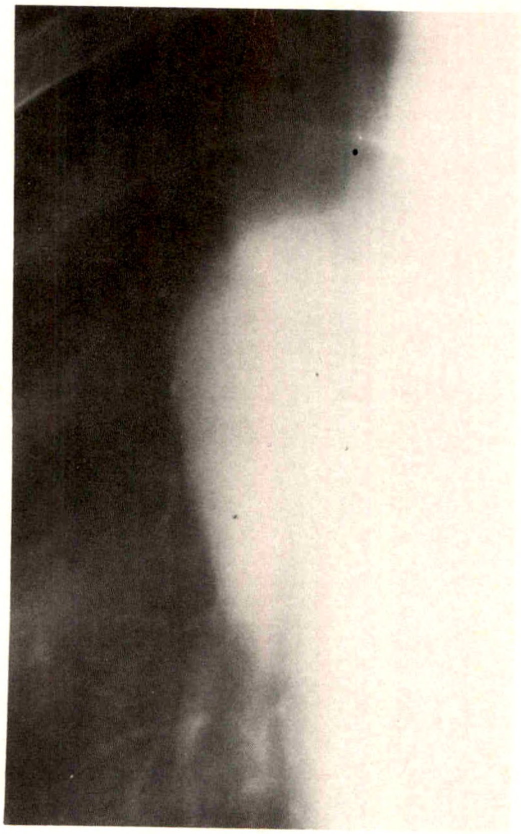

Fig 3. Tomogram of the right paravertebral mass.

mal limits. Bacteriological examination of the sputum showed *Diplococcus pneumoniae* and *Hemophilus influenzae* for which Clamoxyl (amoxicillin) was given. Bronchoscopy with mucosal biopsy revealed a metaplastic and dysplastic epithelium.

On the basis of a clinical diagnosis of bronchial carcinoma, mediastinoscopy was performed. During this procedure, a profuse hemorrhage necessitated thoracotomy. In spite of all measures taken, the patient died. Permission for postmortem examination was not obtained. Histological examination of the biopsy specimens from multiple right paravertebral nodules (maximal diameter, 5 cm) during the surgical procedure showed active hematopoietic tissue consisting of mainly erythroblastic elements (Fig 4).

Comment

Extramedullary hematopoiesis is seen in a variety of diseases as a compensatory phenomenon either to long-standing hemolytic states such as thalassemia, spherocytosis, and pernicious anemia or to bone marrow replacement in conditions like myelofibrosis and extensive neoplastic infiltration of the bones. Blood cell production outside the bone marrow has been reported in the liver, spleen, lymph nodes, kidneys, retroperitoneal tissue, prostate, epididymis, broad ligament, appendix, sciatic nerve, adrenal glands, pleura, lungs, thymus, breast, skin, dura mater of the skull and the spinal canal, and the falx cerebri.

Heterotopic marrow nearly always forms widespread microscopic foci, and the occurrence of tumorlike masses of hematopoietic tissue is uncommon. The most usual site in which the tumorous form of extramedullary tissue is seen is the lower thoracic region [1, 2, 4, 6, 8, 12, 13], but it has also been encountered in the epidural space [9–11, 13] and the retroperitoneal connective tissue [7].

The majority of the cases have been associated with chronic hemolytic states, especially thalassemia [1, 2, 4, 8, 10–13]. Occasionally tumor-simulating extramedullary hematopoiesis has been reported in myelofibrosis [3, 5, 9]. Rarely, masses of extramedullary hematopoietic tissue occur without apparent cause [7], as illustrated by our second patient. Intrathoracic masses of heterotopic marrow occur either unilaterally or bilaterally in the posterior mediastinum, often in the area between the sixth and twelfth thoracic vertebrae. They usually are

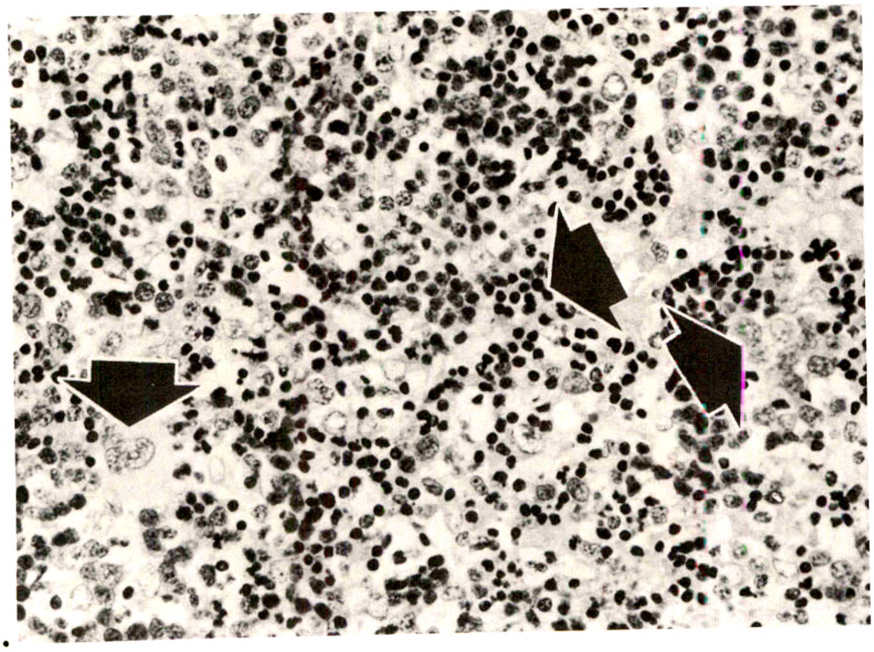

Fig 4. Biopsy specimen of the intrathoracic masses in Patient 2 demonstrating large numbers of normoblasts (upper right arrow). *Members of the white blood cell series* (lower right arrow) *and megakaryocytes* (left arrow) *can also be identified. (H&E; ×350.)*

asymptomatic. However, there is a possibility of spinal cord compression.

Tumor-simulating intrathoracic marrow heterotopia presents a roentgenographic picture that is "typical" [9, 13]. The characteristic feature is that of multiple soft, lobular, well-circumscribed, nonsymmetrical paravertebral masses located in the posterior mediastinum without evidence of calcification, pulsation, or bony erosion. Other findings such as anemia, hepatosplenomegaly, and bony changes that may occur in hemolytic anemia or myelofibrosis can be helpful to make the correct diagnosis. In the differential diagnosis, a neurogenic neoplasm, the most common tumor of the posterior mediastinum, should be considered first. These masses of extramedullary hematopoiesis are highly vascular, and needle aspiration or biopsy can cause a dangerous hemorrhage. Therefore, direct observation at the time of biopsy is preferable. Histopathological examination of these soft, brown, tumor-like masses reveals hematopoietic tissue containing all elements of myelopoiesis and erythropoiesis, including megakaryocytes.

Treatment depends on the location and pathogenesis of the mass of ectopic marrow. When the mass of extramedullary hematopoiesis is a compensatory phenomenon, excision may not be indicated. However, in patients in whom spinal cord compression is developing, surgical decompression is essential. It should be followed by radiation therapy, if necessary, since the extramedullary hematopoietic tissue is highly radiosensitive.

The origin of the extramedullary hematopoietic masses is still unclear, and different explanations have been given. The best theory with respect to the paravertebral, thoracic location is direct extension or herniation of the hyperplastic marrow through a defect in the cortex of the rib or vertebral body [2]. Other possible mechanisms are stimulation of embryonic rests and differentiation of mesenchymal cells still having a potentiality of hematopoiesis.

In patients with bone marrow replacement or long-standing hemolytic anemia, the possibility of marrow heterotopia should be considered when intrathoracic masses are present. However, especially in light of our experience with our second patient, we believe with Kapadia and Kanbour [7] that ectopic marrow should form part of the differential diagnosis of a mass in the lower thoracic region and the retroperitoneum, even in the absence of an apparent cause. Clinicians should be aware of this uncommon condition because mediastinal masses frequently are neoplastic. Therefore, establishment of a diagnosis of extramedullary hematopoiesis may avoid unnecessary operation.

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Internal Mammary–Anomalous Left Anterior Descending Coronary Artery Graft in 16-Month-Old Infant with Tetralogy of Fallot: 30-Month Follow-up

Denton A. Cooley, M.D., Dan G. McNamara, M.D.,
J. Michael Duncan, M.D., and David A. Ott, M.D.

ABSTRACT **Congenital anomalies of the coronary arteries can occur in conjunction with tetralogy of Fallot. We describe a case of unsuspected anomalous origin of the left anterior descending coronary artery arising from the right coronary artery that was discovered at the time of operation in a 16-month-old infant with tetralogy of Fallot. Successful direct vascular repair of the intracardiac anomalies was performed, including left internal mammary–coronary artery anastomosis. The patient, whom we believe to be the youngest to undergo this technique, underwent cardiac catheterization 21 months after operation. The successful results were confirmed at that time.**

Congenital anomalies of the coronary arteries may occur in many forms, such as atresia, aneurysm, and cirsoid formation, in many sites, and in differing distributions. Not uncommonly, anomalous origin of the left or right coronary artery is discovered in conjunction with tetralogy of Fallot and can influence the technique of repair. This report concerns an infant with an unsuspected anomalous origin of the left anterior descending coronary artery arising from the right coronary artery. Direct vascular repair was required, and the result was successful.

On September 26, 1976, a 16-month-old girl weighing 8 kg was admitted to the Texas Children's Hospital because of spells of cyanosis, irritability, and failure to thrive. Physical examination revealed pronounced cyanosis and clubbing, an enlarged right ventricle, a systolic ejection murmur, and a soft, single second sound in the left second space. There were no signs of heart failure. Results of roentgenography and electrocardiography were characteristic of tetralogy of Fallot. Cardiac catheterization was performed September 27, 1976, and revealed findings typical of tetralogy of Fallot with severe elongated infundibular stenosis. An aortic root injection to define the anatomy of the coronary artery was not made, and coronary distribution was assumed to be normal.

Operation was performed September 26, 1976, through the standard median sternotomy approach. Cannulations were made to the venae cavae and to the ascending aorta. When cardiopulmonary bypass was started, the vena cava tape occluders were closed and the ascending aorta was cross-clamped, producing cardiac arrest. As a vertical incision was being made in the outflow tract of the right ventricle, an oversized coronary artery was divided. It crossed the infundibulum and entered the interventricular groove where it descended to the apex of the heart as the left anterior descending coronary artery.

Repair of the intracardiac anomalies was performed through the ventriculotomy, which was extended across the annulus of the pulmonary valve. The valve, which was severely stenotic and deformed with a vegetation on the valve margin, was excised. Infundibular resection was done. A patent foramen ovale was exposed retrograde through the tricuspid valve and closed with a figure-of-eight suture. A knitted velour Dacron patch was sewn over the large ventricular septal defect, and an elliptical, low-porosity woven Dacron patch was inserted in the ventriculotomy to enlarge the infundibular and annular zones.

The proximal end of the divided anomalous

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left anterior descending coronary artery was ligated, and the distal end was probed to confirm that the artery was the blood supply to the anterolateral surface of the left ventricle and ventricular septum. The left internal mammary artery and vein and adjacent tissue were separated from the intrathoracic attachments, and segmental vessels were carefully ligated. Metal clips and electrocautery were used to close the vessels on the chest wall. Papaverine hydrochloride was applied to the mammary artery, which was 1.0 mm in diameter. This produced dilatation and free flow of blood from the divided end. An end-to-side anastomosis was performed to the coronary artery using 7-0 monofilament polypropylene suture. Since the aortic clamp was still in place, the heart was in total ischemic arrest. As the internal mammary artery was released, coronary flow was reestablished and cardiac action resumed immediately, confirming the presence of a patent anastomosis.

Cardiopulmonary bypass, which had been performed using fresh heparinized blood (500 ml), 5% dextrose in Ringer's lactate solution (300 ml), and sodium bicarbonate (20 mEq) to prime the pump, was discontinued. A bubble diffusion oxygenator had been used, and the patient was maintained normothermic throughout the procedure. Ischemic cardiac arrest without cardioplegic solution was used for 56 of the 61 minutes of perfusion.

The patient made an uneventful recovery and was discharged from the hospital two and one-half weeks later. Her health and development have been normal since that time, and periodic examinations have been made in this clinic.

Postoperative Cardiac Catheterization Data

Site	Pressure (mm Hg)	Blood Oxygen Saturation (%)
Superior vena cava	$\overline{2}$	74
Right ventricle	30/0–5	73
Pulmonary artery	18/4, $\overline{10}$	73
Femoral artery	78/45, $\overline{60}$	96

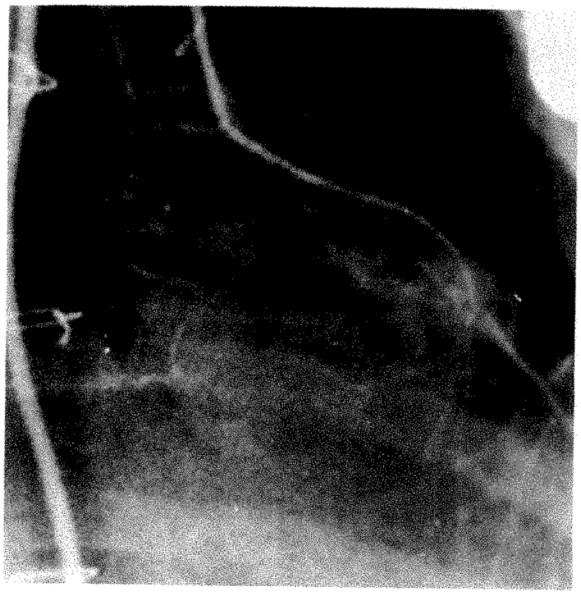

Fig 1. Postoperative selective injection into the left internal mammary artery (injection site not shown) reveals filling of the left anterior descending artery in this anteroposterior view.

Cardiac catheterization was repeated at the Medical University of South Carolina* on June 9, 1978, 21 months after operation. It revealed excellent hemodynamics and no evidence of an intracardiac shunt (Table). Injection into the left internal mammary artery confirmed patency of the mammary–coronary artery anastomosis (Fig 1). Aortic root injection showed filling of the right coronary artery and the circumflex artery without filling of the left anterior descending coronary artery (Fig 2).

Comment

According to Fellows and co-workers [5], the incidence of coronary artery anomalies in patients with tetralogy of Fallot, as determined by aortography, is 5%. Among 84 patients they studied, 4 had anomalous origin of the left anterior descending coronary artery from the right coronary artery. Among 195 patients with tetralogy of Fallot they examined postmortem, the incidence of coronary artery anomalies was 5%. Three of these patients had origin of the left anterior descending artery from the right coronary artery. Of the 94 patients studied, a satisfactory aortogram was recorded in only 84. It is

*By Arno R. Hohn, M.D., Director, Division of Pediatric Cardiology, Medical University of South Carolina, Charleston, SC.

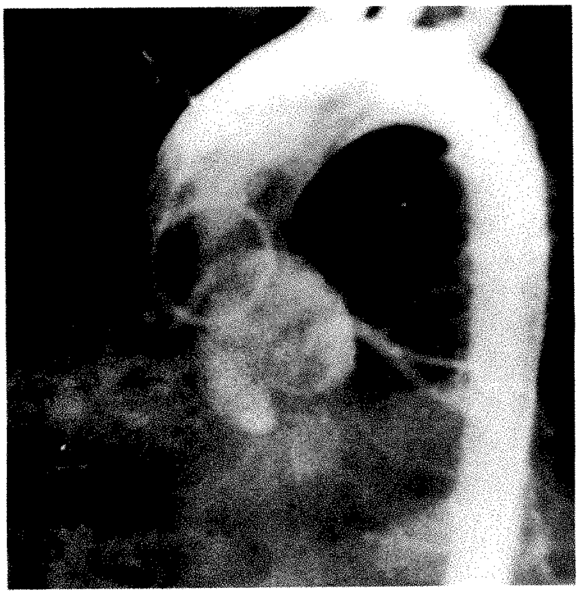

Fig 2. Postoperative left anterior oblique view of an aortic root aortogram after injection through a coiled, pig-tailed catheter shows filling of the right coronary artery and the circumflex artery. The left anterior descending artery is not filled.

not always possible in a young infant to obtain an aortic root angiogram of sufficient quality to delineate clearly the coronary artery anatomy.

When this anomaly is present, the standard direct approach to the intracardiac defects, i.e., through a ventriculotomy in the outflow tract of the right ventricle, must be modified. Previously, in some patients we have recommended indirect or palliative measures, such as, creating systemic-pulmonary shunts to avoid possible complications particularly in small infants. We have also described and used methods of reconstructing the outflow tract with patch grafts or conduits to avoid the artery entirely [3]. However, in the present patient, the artery was divided before the presence of the anomaly was appreciated. Moreover, the use of an outflow conduit graft in a 16-month-old child may not have been satisfactory, even if the situation had been identified before operation, because of future growth of the patient.

Successful direct coronary operation for coronary anomalies actually preceded the application of such techniques to acquired disease [2, 8]. Fifteen years ago, we recommended reconstructing a two-coronary system for patients with a single left coronary artery or anomalous origin of a left coronary artery using a Dacron graft or saphenous vein graft. Following early reports by Favaloro [4] in 1968 and Johnson and colleagues [9] in 1969, who pioneered the use of autologous saphenous vein grafts for coronary bypass of atherosclerotic occlusions, the technique became almost standard surgical treatment. Green and associates [6] soon perfected the technique of an internal mammary pedicled graft for revascularization, particularly the left anterior descending coronary artery. This method has proved to provide superior long-term patency when compared with the autologous saphenous veins and the internal mammary artery graft and does not develop degenerative changes as quickly or to the same degree as the saphenous vein. Recent reports indicate that the internal mammary artery anastomosis, while more tedious than the saphenous vein, will provide a better prognosis for long-term patency and function [10–12]. The reason for this difference may be that the wall of the pedicled internal mammary artery has its own supply of blood and intact vasa vasorum to maintain its viability, while the saphenous vein is a free graft, which must establish a new blood supply from surrounding tissues. Sequential vein grafting using side-to-side anastomoses, however, appears to enhance the ability of saphenous veins to remain patent over a long term [1, 7]. The choice of the internal mammary artery in this 16-month-old child, whom we believe is the youngest patient to undergo this technique, was influenced by these considerations.

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Notice from the American Board of Thoracic Surgery

The American Board of Thoracic Surgery now requires that candidates pass both the written and oral portions of the certifying examination.

In 1980 and thereafter, a written examination will be given *prior* to the oral examination. It will be necessary to pass the written examination before the oral examination can be taken. The closing date for registration for 1982 is August 1, 1981. The exact times and places of these examinations will be announced later.

A candidate applying for admission to the 1982 certifying examination must fulfill all the requirements for the Board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, 14640 E Seven Mile Road, Detroit, MI 48205.

Early Calcification and Obstruction of a Mitral Porcine Bioprosthesis

Basil S. Lewis, M.D., Avinoam Bakst, M.B., B.Ch.,
Joe L. Rod, M.B., B.Ch., Azaria Rein, M.D.,
Mervyn S. Gotsman, F.R.C.P., and Azai Appelbaum, M.D.

ABSTRACT **A patient is described in whom severe prosthetic valvular stenosis developed ten months after mitral valve replacement with an Angell-Shiley porcine heterograft. At emergency operation, calcification of the prosthesis was revealed. Early calcification and stenosis of a porcine heterograft valve is a life-threatening complication that must be recognized promptly and treated by emergency valve replacement.**

Valve replacement with a mounted porcine heterograft produces a good hemodynamic result and a low incidence of thromboembolic complications and hemolysis [1, 3, 4, 10, 12]. The durability of these valves is uncertain, however, and their life span is limited because of changes that occur in the valve cusps after preparation and implantation.

This report describes a patient who underwent successful mitral valve replacement using an Angell-Shiley glutaraldehyde-treated mounted porcine bioprosthesis. However, early and severe mitral stenosis, with calcification and rigidity of the leaflets, occurred ten months after operation. Emergency operation was undertaken and the mitral valve replaced.

A 17-year-old boy had a four-year history of shortness of breath with progressive deterioration to grade 3 disability. When he was 7 years old, he had been hospitalized for one and a half months for acute rheumatic fever with carditis. On examination he had the features of severe mitral incompetence and severe pulmonary artery hypertension. The mitral valve was replaced with a 31 mm Angell-Shiley mitral bioprosthesis. The postoperative course was uneventful, and the patient was discharged ten days after operation. At an early postoperative visit, the symptoms had improved greatly, and the patient was only mildly disabled (grade I to IIa). He was able to run around freely and had returned to a fairly normal existence.

Ten months postoperatively, the patient again complained of severe shortness of breath, palpitations, and hemoptysis, with progressive limitation over a three- to four-week period to grade IV disability. Treatment with digoxin (0.25 mg daily), furosemide (80 mg daily), and spironolactone (25 mg four times per day) did little to relieve the symptoms. On examination he was thin, cyanotic, and short of breath at rest. The pulse was 90 beats per minute, irregular, and small in volume. The blood pressure was 110/60 mm Hg. The jugular venous pressure was raised to the angle of the mandible with a large v wave and normal y descent. The apex was in the fifth interspace in the midclavicular line, and on auscultation, a normal first heart sound, a loud pulmonary component of the second sound, and a medium length diastolic rumbling murmur at the apex were revealed. A pansystolic murmur was audible near the left sternal border and increased on inspiration. The clinical diagnosis was mitral stenosis with severe pulmonary hypertension and tricuspid incompetence.

The electrocardiogram showed atrial fibrillation, a mean frontal QRS axis of +70 degrees, and right and left ventricular hypertrophy. The chest roentgenogram showed a cardiothoracic ratio of 0.55, grade III left atrial enlargement, severe pulmonary venous hypertension with interstitial edema, and severe enlargement of the right ventricle and pulmonary artery. The echocardiogram showed an increase in left atrial diameter compared with the immediate postoperative study (Table). There was no

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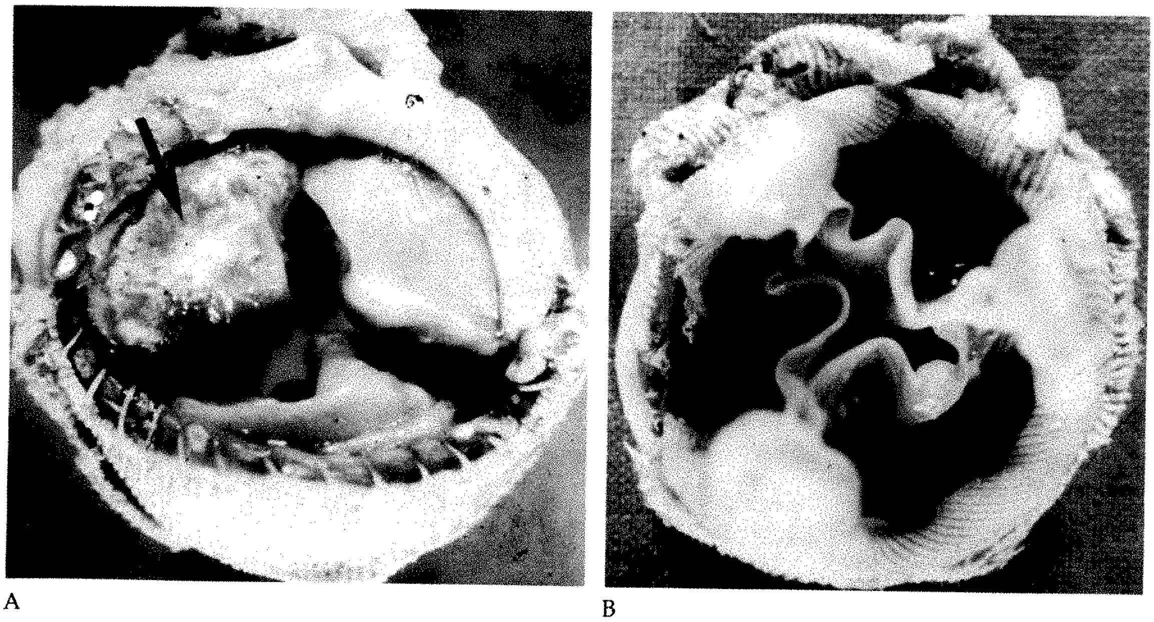
Echocardiographic Measurements

Measurement	2 Weeks after First Operation (Angell-Shiley Valve)	10 Months Later	After Reoperation (Björk-Shiley Valve)	Normal Values
Left atrial dimension (cm)	6.1	8.2	5.7	3.3 ± 0.5
LV end-diastolic dimension (cm)	5.5	5.5	5.6	5.0 ± 0.4
Peak normalized LV filling rate (sec^{-1})	1.84	0.85	2.02	4.3 ± 1.0

LV = left ventricular.



Excised porcine heterograft. (A) Atrial surface, showing heavy calcification and ulceration in one of the leaflets (arrow). *There were smaller areas of calcification in the other cusps. (B) Ventricular surface. There is distortion of the leaflets with infolding of the edges caused by scarring and calcification.*

change in left ventricular size but peak left ventricular filling rate, calculated by digitizing the echocardiogram [13], was decreased, and the time to peak filling was prolonged. The leaflets of the mitral prosthesis were not visualized. Cardiac catheterization confirmed the diagnosis of severe mitral stenosis. The pulmonary capillary wedge pressure was 35 mm Hg, and the mitral mean diastolic gradient was 26 mm Hg at a heart rate of 85 beats per minute. The pulmonary artery pressure was 70/35 mm Hg, the cardiac index was 3.6 L/min/m^2, and the ratio of pulmonary vascular to systemic vascular resistance was 15%. Left ventricular angiography showed a normal-sized left ventricle, which contracted well with no mitral incompetence.

An urgent second operation was undertaken, and the Angell-Shiley bioprosthesis was replaced with a Björk-Shiley 27 mm tilting-disc prosthesis. The postoperative course was uneventful, the patient's symptoms again receded rapidly, and he was discharged from the hospital two weeks after the second operation. Postoperative echocardiography showed a decrease in left atrial size and an increase in the left ventricular filling rate (see Table).

The excised Angell-Shiley valve had fibrosis and calcification of the leaflets (Figure). Valve opening was limited markedly. Histological examination showed fibrosis and calcification of all three leaflets.

Comment

The usual determining factor of the durability of a porcine heterograft bioprosthesis, as with all bioprostheses, is the appearance of valvular incompetence following leaflet perforation or loss of substance. The valve is inert after preparation, and there seems to be little fibroblastic ingrowth of host tissue. Following implantation of the valve, there is insudation of plasma proteins into the substance of the leaflets, penetration of erythrocytes and leukocytes, and loosening of the arrangement of the collagen bundles in the leaflets. Collagen disruption progresses with time, and the extent to which this change occurs has been related to the length of time the valve is in place [2, 5]. The collagen degeneration may be followed by thinning and perforation of the leaflets.

The porcine heterograft also has been associated with overgrowth of tissue causing fibrosis, rigidity, calcification, and stenosis [7–9, 11]. However, these changes usually have developed later than the ten months during which prosthetic valvular stenosis occurred in our patient or in patients with systemic diseases which may be associated with abnormalities of calcium metabolism [8]. There is a report of very early calcification and stenosis of a Carpentier-Edwards prosthesis eighteen days after its implantation in a patient with infective endocarditis, but this may have been due to a defect in the valve before insertion [6].

The diagnosis of prosthetic valvular dysfunction may be difficult clinically, but patients who do well in the immediate postoperative period and then deteriorate must be investigated carefully. Soft systolic and diastolic murmurs have been observed in apparently normally functioning porcine heterograft valves, but exaggeration of these murmurs, persistence of pulmonary artery hypertension, right heart failure, and important clinical cardiac disability may be due to prosthetic valve incompetence or stenosis. Important residual cardiomegaly and pulmonary venous hypertension on the chest roentgenogram provide further evidence for the diagnosis. The echocardiogram may show decreased excursion of the prosthetic valve leaflets, an increasing left atrial size, and a change in the left ventricular filling rate in early diastole. Cardiac catheterization is diagnostic. Patients with suspected prosthetic valvular dysfunction must be investigated promptly to confirm or refute the diagnosis since early reoperation for patients with prosthetic valve dysfunction is lifesaving.

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Utilization of the Free Wall of the Left Ventricle for Repair of Septal Rupture after Infarction

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and R. O. Heimbecker, F.R.C.S.(C)

ABSTRACT **Two cases of ventricular septal defect following myocardial infarction are presented. An innovative technique of free ventricular wall rotation was used for surgical repair and is described here. The indications for the use of this technique are discussed, and its advantages over conventional methods of repair are reviewed.**

Acute rupture of the interventricular septum following myocardial infarction is a catastrophic complication carrying a 50% mortality in the first week [8]. Various emergency surgical procedures have been described, the techniques ranging from distal amputation of the heart, where the defect is distally placed, to reconstruction of the muscular septum by patching procedures secured by various suturing techniques [4].

When repair can be deferred for twelve weeks or longer to allow good fibrous tissue margins to form in the defect, the operative procedure is usually straightforward and satisfactory [2–6]. When the patient is deteriorating rapidly, urgent repair often has to be carried out in the first few days. Under these circumstances, the necrotic margin takes sutures very poorly. This results in a very high incidence of repair breakdown and ensuing operative mortality. It is in this emergency group in whom early operation becomes mandatory that we have found the technique presented here to be of considerable value.

Patient 1

A 67-year-old woman was hospitalized on April 2, 1975, with an acute anteroseptal myocardial infarction. The patient's convalescence was uneventful until the development of a pansystolic murmur along the lower left sternal border five weeks later. The onset of this murmur heralded an abrupt deterioration in the clinical course. Increasing intensity of the systolic murmur was accompanied by the sudden onset of severe intractable biventricular failure. This clinical event suggested the possibility of extension of a preexisting infarction with the development of an acute rupture of the interventricular septum.

The patient was transferred to University Hospital in London, Ontario, for further investigation. The prominent clinical feature was a loud apical pansystolic murmur with wide radiation to the left axilla and to the back, associated with a systolic thrill and a right ventricular lift. The electrocardiogram revealed changes of an acute anteroseptal infarction with left anterior hemiblock. Severe congestive heart failure persisted in spite of intensive medical treatment.

Cardiac catheterization on May 16, 1975, disclosed the presence of a large ventricular septal defect associated with a torrential left-to-right shunt (8.3:1). The left ventricular angiogram further demonstrated moderately severe left ventricular dysfunction with akinesis of the apex and adjacent anterolateral wall. Selective coronary injection demonstrated occlusion of the left anterior descending coronary artery immediately distal to the diagonal branch, in association with a normal dominant right coronary artery and a mildly diseased circumflex system (Table).

Surgical repair of the acute ventricular septal defect was performed on May 17, 1975, six weeks following the initial anteroseptal infarc-

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Catheterization Data

Determination	Preop: 16/5/75[a]	Postop: 28/5/75[b]
Aorta (mm Hg)	105/70	135/60
LVP (mm Hg)	105/28	135/14
LVEDP (mm Hg)	28	14
RAP (mm Hg)	19	9
RVP (mm Hg)	90/22	42/12
PAP (mm Hg)	90/30	42/12
CO (Fick) (L/min)	3.2	3.3
Shunt	8.3 : 1	Nil

[a] Preoperatively, the patient had a large ventricular septal defect, severe left ventricular dysfunction, and pulmonary hypertension.
[b] Postoperatively, left ventricular function was improved and there was no shunt.

LVP = left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; RAP = right atrial pressure; RVP = right ventricular pressure; PAP = pulmonary artery pressure; CO = cardiac output.

tion and promptly after the development of a murmur and intractable heart failure. Utilizing median sternotomy and standard techniques of cardiopulmonary bypass, moderate hypothermia to 30°C was induced and the vented heart was then electrically fibrillated.

A paraseptal incision in the anterior wall of the left ventricle along its long axis revealed the presence of a large septal defect with a freshly necrotic margin located high in the anterior muscular portion of the ventricular septum. Because of the extent and proximal location of the defect and the adjacent nonviable septum, conventional techniques of repair, including distal cardiac amputation, were clearly inappropriate. Following wide excision of the necrotic margin of the defect, the free anterolateral wall of the left ventricle was rotated and advanced and sutured to the posterior rim of the septal defect with interrupted, pledgeted mattress sutures, thereby fashioning a new interventricular septum out of the left ventricular wall (Figure). The vented left ventricle was then defibrillated and the suture line determined to be hemostatic with the heart beating. The free wall of the right ventricle was then approximated to the advanced left ventricular wall by means of a continuous suture. Caval tapes were released and a hemostatic right ventricle–left ventricle suture line ensured. The electrocardiogram showed no interference with the cardiac conduction system.

The patient made an uneventful postoperative recovery free from rhythm problems and without cardiac failure. The postoperative catheter study demonstrated normal hemodynamics with no evidence of left-to-side shunting or mitral insufficiency (see Table). It has now been more than five years since this operation, and the patient is asymptomatic with excellent exercise tolerance and no cardiac failure or angina.

Patient 2

A 55-year-old man was found to have a large high posterior defect of the muscular septum. It was repaired by a posterior ventricular incision in which the necrotic areas of the defect were radically excised. Then the posterior free wall of the left ventricle was rolled in to close the defect. Multiple mattress sutures resulted in a secure and satisfactory closure. This repair was a mirror image of the operation in Patient 1 in which the anterior free wall of the ventricle was utilized because of the anterior position of the septal rupture.

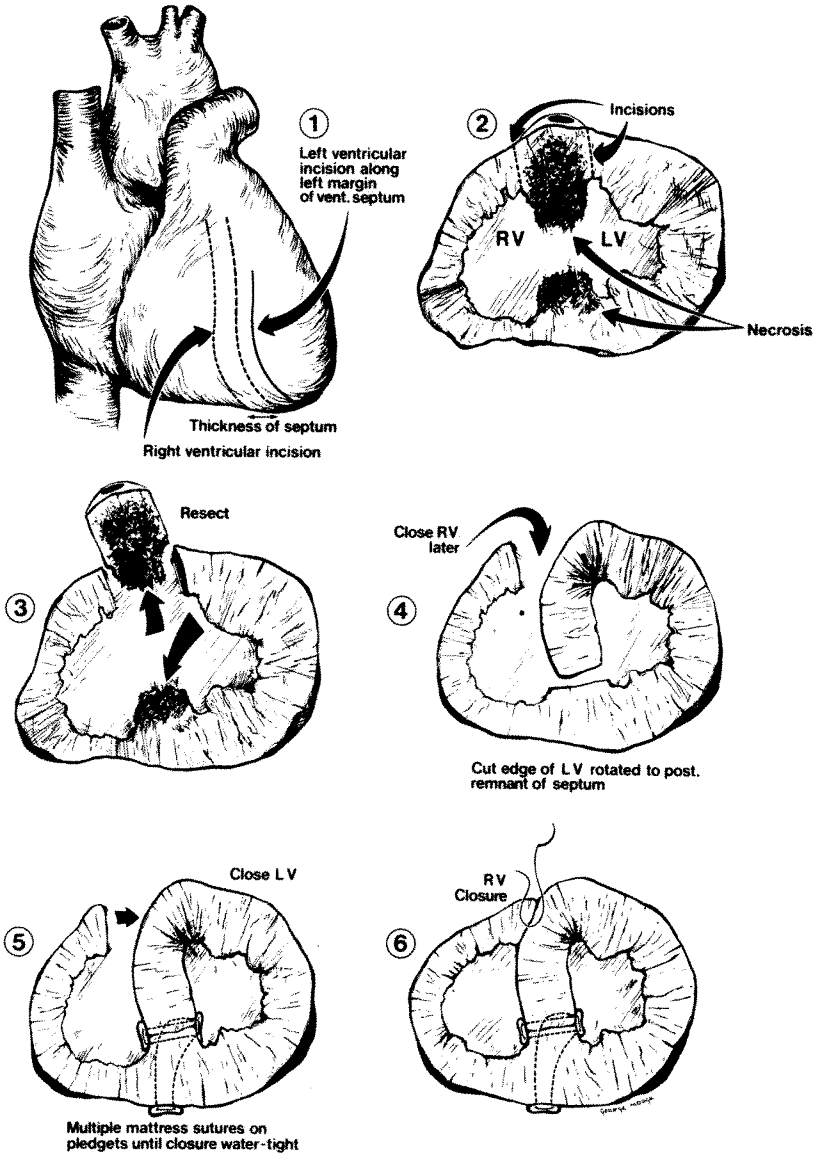
Postoperatively, the patient has remained free from murmur and is enjoying normal health without evidence of cardiac failure or angina.

Comment

The development of an interventricular septal defect following myocardial infarction is an extremely grave situation occurring in about 1% of patients [10]. The early mortality is high: about 50% of patients die within the first week and 30% within the following two months [8].

Successful closure of a septal rupture was accomplished by Cooley [3] in 1957 and since that time many small series have been reported [1, 2, 5, 7, 9, 12]. Various techniques have been used depending on the location of the perforation. According to Swithinbank [11], two-thirds of perforations will occur in the lower anterior septum and therefore should be quite amenable to distal cardiac amputation as proposed by Daggett and colleagues [4].

Defects located more proximally in the septum call for alternative procedures. Gerbode


①
Left ventricular incision along left margin of vent. septum
Thickness of septum
Right ventricular incision
②
Incisions
RV
LV
Necrosis
③
Resect
④
Close RV later
Cut edge of L V rotated to post. remnant of septum
⑤
Close L V
Multiple mattress sutures on pledgets until closure water-tight
⑥
R V Closure

The steps in mobilization and rotation of the free wall of the left ventricle (LV) *and closure of the ventricular septal defect.* (RV = *right ventricle.)*

and associates [6] described an innovative approach utilizing the right ventricular wall to embrace and buttress the Teflon patch closure of the ventricular septal defect. However, this technique does not completely avoid the problem of suturing poor-quality tissue. Furthermore, it is anticipated that this technique would result in an unacceptable degree of compromise of the right ventricle in the event of a large septal rupture, as in our patients. It is in this group that we found this new technique of utilizing the free wall of the left ventricle to provide a satisfactory hemostatic closure. Damage to the ventricular conduction system during repair was not encountered in either patient, this potential hazard being minimized by limiting resection to only necrotic septal muscle. Postoperative catheterization and clinical follow-up of more than five years attest to the efficacy of this method.

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Pacemaker Implantation in Infants and Children: A Simplified Approach

Serafin Y. DeLeon, M.D., Michel N. Ilbawi, M.D., and Farouk S. Idriss, M.D.

ABSTRACT **A technique for epicardial pacemaker implantation is described. A single incision is utilized through which the electrode and power pack are implanted. Twelve infants and children were operated on in the last four years using this procedure. The marked improvement in cosmetic appearance and the relative ease in module replacement are major advantages of this method.**

Pacemaker implantation in infants and children is required occasionally and may present some technical difficulties. Limited space for the power pack and lead, scanty subcutaneous tissue, and allowance for growth are some of the considerations in this age group. Normally, epicardial pacing is used since intravenous implantation of pacing leads is not practical. It also is necessary to feed more wire into the neck vein as the child grows [9]. Numerous published reports describe the technique for epicardial implantation in children [1–3, 6–8, 10]. Intrapleural, subcutaneous, intermuscular, and properitoneal placements of the power pack have been suggested. The epicardial electrode is usually implanted through a separate thoracotomy incision when the power pack is inserted in a pocket over the abdominal area. Idriss and colleagues [5] reported the use of permanent pacemakers in the first month of life and put the unit in the abdominal subcutaneous space.

In order to minimize the unsightly bulge, problems with skin erosions, and multiple incisions, we have adopted a new technique that employs a single incision through which both the epicardial electrode and the power pack are implanted. The approach is particularly advantageous in postoperative patients in whom a small extension of the median sternotomy scar is sufficient. Reoperation for electrode and power pack replacement is relatively simple. Twelve children ranging from 4 months to 14 years old were operated on using this technique in the last four years.

Technique

The patient is placed in the supine position (Fig 1). Either a midline subxiphoid incision is made or in patients who have already undergone operation, the lower end of the midsternotomy scar is reopened and extended toward the umbilicus. The incision is made slightly longer than the diameter of the power pack. The linea alba is opened, leaving the peritoneum intact. A suitable area of the heart is selected, and the epicardial electrode is implanted. In the majority of patients this is over the diaphragmatic surface of the right ventricle, but the anterior surface of both right and left ventricles has also been utilized. The lower end of the sternum may be split to gain better exposure, especially in patients who have had a previous intracardiac repair.

After a satisfactory pacing threshold is obtained, the pocket is made. The rectus space is entered on both sides, and the muscle belly is separated from the posterior rectus sheath. The posterior rectus sheath is then approximated, and the power pack is placed between the muscle mass and the posterior rectus sheath. The anterior rectus sheath, subcutaneous tissue, and skin are approximated. A few sternal sutures may be needed if the lower end has been split.

Comment

Since we abandoned the subcutaneous implantation of the pacemaker power pack and switched to the present technique, we have encountered no problems with skin erosions. The result is cosmetically acceptable (Fig 2), and the

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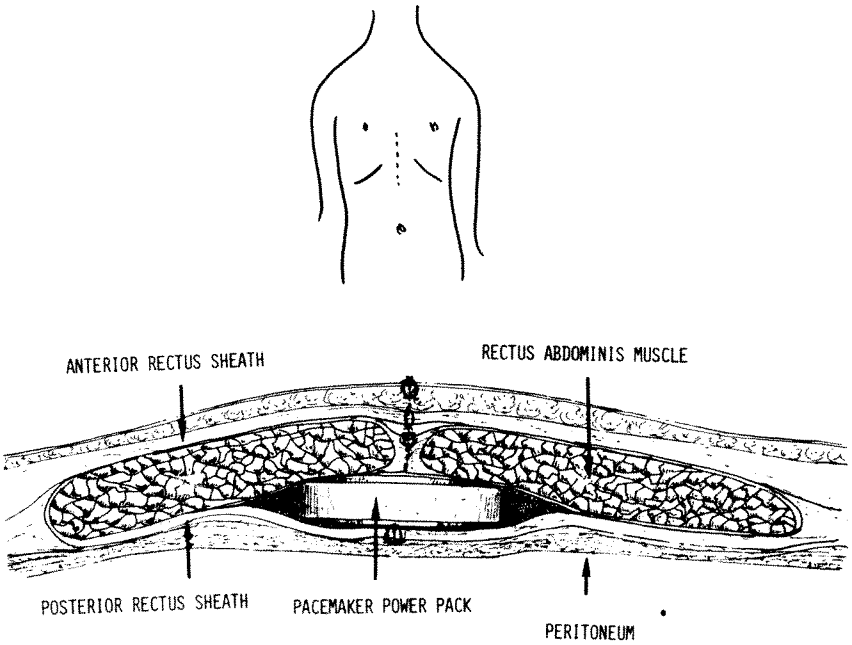

Fig 1. Midline incision through which the pacemaker electrode and power pack are implanted. The power pack is placed inside the rectus sheath between the muscle belly and the posterior rectus sheath. The peritoneum is left intact. The location of the incision over the power pack facilitates replacement.

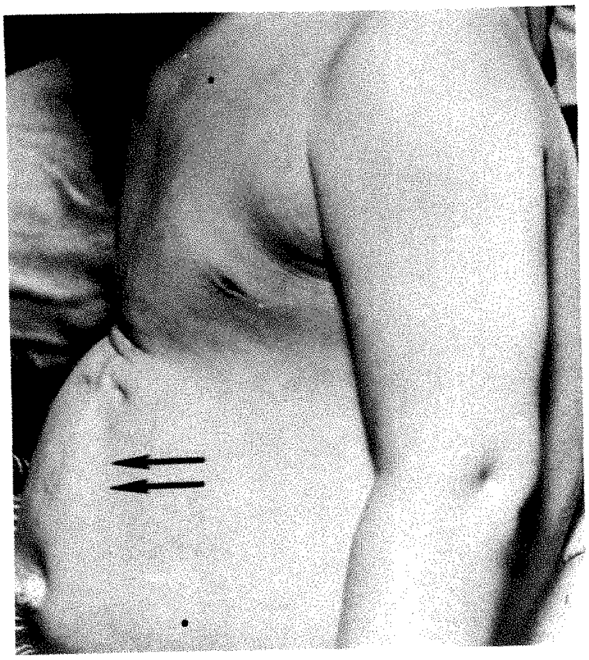

Fig 2. One-year-old boy who had epicardial pacemaker implantation when he was 4 months old because of complete heart block after repair of a ventricular septal defect. The power pack is indicated by the arrows.

child can wear a belt. This was avoided before for fear of skin erosions. No unnecessary scars are made since both pacemaker lead and power pack are implanted through a single incision. When a midsternotomy scar is present, it is extended downward. Previously, patients with pacemakers and with postoperative heart block would end up with two or more incisional scars [1–3, 5, 10]. Since the incidence of electrode failure is high in the pediatric age group [4], the ease of electrode removal and reimplantation becomes a technical consideration. Exit block developed in 3 of the 12 patients one to four months after implantation. All or most of the old electrode was removed and a new one implanted.

Reoperation through a previous thoracotomy incision is relatively more difficult. Exposure is limited, lung adhesions have to be taken down, and a chest tube is often required. Pulmonary air leaks from lysis of adhesions may predispose to infection, especially in the presence of a foreign body. Although Donahoo and coworkers [3] reported a reluctance to using the right ventricle due to its thinness, our experience seems to differ. Two of the 3 patients who had electrode malfunction had thick right ventricles. One had tetralogy of Fallot and the other, transposition of the great arteries.

This technique we describe offers a good cosmetic appearance, obviates extra incisions, and provides relative ease in pacemaker electrode and power pack replacement.

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COLLECTIVE REVIEW

Small Cell Carcinoma of the Lung

John A. Meyer, M.D., and Frederick B. Parker, Jr., M.D.

ABSTRACT **Prospects for the patient with small cell carcinoma of the lung have been partially turned around during the past decade. This dramatic achievement remains very incomplete, but it continues to gather momentum and seems to carry promise of greater advance in the future. An essential feature of the new approach to treatment is that it depends on cooperative and interdisciplinary effort; in all probability, increasing cooperation will be necessary for future progress. We will attempt to review here the current approaches to the understanding and management of this disease, as they may be of concern to surgeons, and to try to define the areas of failure and controversy.**

Small cell carcinoma was one of the two principal tumor types of the "Bergkrankheit" or mountain disease, the lung cancer of the pitchblende and uranium miners of Bohemia and Saxony in central Europe. The disease was recognized clearly in the nineteenth century as being of occupational origin. In early reports the tumor was identified as a sarcoma, akin to "lymphosarcoma," but eventually it was recognized as a highly anaplastic carcinoma [1]. The last definitive review in English of the miners' cancer may have been that of Lorenz [2]; careful epidemiological studies have been hampered in recent years by world political tensions. The area of the mines lay at first on the border between Germany and Austria-Hungary, and after World War I, between Germany and Czechoslovakia. After the Munich agreement of 1938, the area was entirely under the control of Hitler. Following World War II, it came under the new political systems of the People's Republic of Czechoslovakia and the German Democratic Republic. It has remained an important producer of uranium in the atomic age. The Bergkrankheit of the nineteenth century remains an occupational health problem; a postwar review of the subject in German listed 55 cases in 1969 [3]. The disease plays no ideological favorites; lung cancer of uranium miners is an occupational hazard in the western United States [4, 5]. Smoking and radioactive dust inhalation remain the known etiological factors, and the two factors are very strongly synergistic [5]. Squamous cell carcinoma is similar in that it is caused by either or both of these etiological factors.

Thorough histological study of this tumor in recent years has classified it into the "oat cell" type and the "intermediate" cell types. Oat cell tumors are made up of uniform small round cells with scanty cytoplasm; these are the closest to lymphocytes in appearance. Intermediate cell types are somewhat larger, with more elongated nuclei and fusiform, spindle-shaped, or polygonal cell contours. There is no demonstrable difference between these cell types in their response to treatment [6]. The "mixed histology" type, however, contains elements of both small cell and large cell anaplastic carcinoma; the rates of response to therapy and of complete remission of these tumors are distinctly poorer than those of the pure small cell tumors [7]. Small cell tumors are highly cellular in histological sections, showing numerous mitoses, many small areas of necrosis, vascular invasion, and marked invasiveness at tumor margins. Widespread lymphatic and hematogenous dissemination are almost always present at the time of diagnosis.

Together with bronchial carcinoid tumors, small cell carcinoma arises from the argentaffin or Kultschitzky cells in bronchial mucosa [8]. Both tumors are members of the APUD group, named for their ability to synthesize polypeptides with hormonal activity: amine precursor uptake and decarboxylation [9]. Other APUD tumors, for example, are pheochromocytomas; neuroblastomas; gastrin-secreting tumors of pancreatic islets; and medullary carcinomas of the thyroid. Among primary lung can-

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cers, small cell carcinomas are perhaps the most active in producing the paraneoplastic or endocrine-like syndromes; Cushing's syndrome and the syndrome of inappropriate antidiuretic hormone secretion are almost always of small cell origin.

Small cell carcinomas appear to have the highest labeling indices [10] and the shortest volume-doubling times among lung tumors. These features, correlating with extreme biological malignancy, may have proved to be the Achilles' heel of this tumor since they also tend to correlate with responsiveness to chemotherapy. While the median volume-doubling times of all lung cancers appear to be in the range of about 80 to 90 days [11–13], several studies of small cell carcinoma have recorded median doubling times in the range of 23 to 40 days [14–16]. Another study reported a median doubling time for small cell carcinoma of 77 days [17]; conceptually this does not appear to fit well with the tumor's highly malignant behavior, and the discrepancy between these findings is not easily explainable.

The Way It Was

By the late 1960s, it was quite apparent that surgical resection did nothing to alter the rapidly lethal course of this disease. Widespread dissemination at the time of diagnosis was obviously responsible; a very few exceptions to this general principle were noted by Higgins and co-workers [18]. Of 889 undiagnosed solitary peripheral pulmonary nodules resected in men, 11 were small cell carcinomas. Among the 11 patients, 4 lived 5 years and 2, 10 years. This study proved only that small cell carcinoma, like other tumors, passes through a Stage I in its life history and that in a tiny fraction of patients it is caught and treated in this stage. Mountain [19] reviewed 41 patients treated by surgical resection at the M. D. Anderson Hospital, without a single long-term survivor. Fifteen of these patients could be classified retrospectively as having had tumors in Stage I and 5 more in Stage II.

During the 1960s, the Medical Research Council of Great Britain conducted a prospective comparative clinical trial of surgical resection versus radiation therapy [20, 21]. There were two criteria for acceptance of patients into the study: (1) a biopsy diagnosis of small cell carcinoma must be available, and (2) the lesion must be declared operable by the surgical consultants. Parenthetically we should note that these patients could not have been studied carefully for distant metastatic disease as patients are today. Randomization assigned 71 patients to be treated by surgical resection and 73 by radiotherapy. Of the patients assigned to radiotherapy, 4 survived for 5 years and 3 for 10 years. The only long-term survivor in the group assigned to resection was a patient who refused resection, was treated by radiotherapy instead, and died at 8 years.

Takita and colleagues [22] reviewed 161 patients treated at the Roswell Park Memorial Institute, by all available modalities, during the 12-year period 1960 through 1971. Median survival was 4.6 months. One patient treated by surgical resection and the experimental drug AB-132 died of recurrence at 77 months; another treated by radiotherapy and hexamethylmelamine remained in complete remission at 38 months, and may have had eradication of disease.

During the 1960s, the Veterans Administration Lung Group treated large numbers of patients with inoperable lung cancer of all cell types by randomization to single-drug chemotherapy regimens. Green and associates [23] found that treatment with cyclophosphamide did not prolong survival in the patient group as a whole. When treated patients were separated by cell type, however, a significant prolongation of median survival from 1.7 to 4.0 months was noted for small cell carcinoma. This and other studies established the principle that small cell carcinoma is a tumor generally responsive to chemotherapy.

Some Principles of Chemotherapy

In a general review of this topic, it seems appropriate to consider some of the basic differences in concepts between oncologists and surgeons. First and perhaps most fundamental, surgeons are conditioned to thinking of their mode of cancer treatment as a one-shot eradication of all the visible bulk of the tumor. In fairness, we must concede that it is usually

Table 1. Theoretical Scheme of the Logarithmic Reduction of Tumor Burden by Perfectly Effective Chemotherapy[a,b]

Tumor Cells	Tumor Bulk	Tumor Weight
10^{12} cells	10 cm tumor diameter	1 kg
10^{9} cells	1 cm diameter	1 gm
Complete remission[c]		
10^{6} cells	1 mm diameter	1 mg
10^{3} cells	1,000 cells	
10^{0}	1 cell	
10^{-1}	Tumor eradication in 90% of cases	
10^{-2}	Tumor eradication in 99% of cases	

[a] A patient with a far advanced incurable malignancy carries a tumor burden roughly on the order of 10^{12} tumor cells. In the aggregate, this is equivalent to a single tumor mass approximately 10 cm in diameter and weighing approximately 1 kg.

[b] The fallacy of this scheme is that it cannot indicate at what point the remaining cell population will be made up of resistant clones.

[c] A three-log or greater reduction of initial tumor bulk is generally sufficient to achieve clinically complete remission since visceral tumors ordinarily are not detectable clinically at a gross diameter of less than 1 cm.

systemic dissemination that defeats our treatment and dooms the patient. We deal with a treatment modality that oncologists consider "local," i.e., without systemic effect.

The primary attribute of chemotherapy, on the other hand, is that no matter how effective it may be against a given tumor, it kills tumor cells by first-order kinetics. This means that a given cycle of chemotherapy will kill, at best, only a set percentage or proportion of the patient's tumor cells, never a given bulk or weight of the tumor. As a tumor responds, its bulk becomes less; therefore, the number of tumor cells killed by subsequent cycles will diminish also. It follows that an equal chemotherapeutic effect is required to reduce a microscopic burden of 1,000 surviving tumor cells to 1 cell, as is required to reduce a gross tumor 10 cm in diameter to a tumor residual 1 cm in diameter (Table 1). Both responses constitute a "three-log" or thousandfold reduction of tumor burden. In the end, it is likely that preexisting or mutant clones of tumor cells, resistant to the chemotherapy, will grow out again and result in relapse.

We ask indulgence for a digression at this point. Zeno of Elea, about 450 BC, put to his students a set of four paradoxes which remained insoluble in logic until development of the calculus. The most easily visualized of the paradoxes can be stated as follows: An archer stands up to the line, draws his bow, and releases an arrow at the target. The arrow first travels half the distance to the target, then half the remaining distance, and so on. It follows that the arrow can never reach the target. For the medical oncologist, Zeno's paradox is not just an intriguing fallacy of logic but a hard and inescapable fact of life. The few exceptions only go to prove the rule.

While surgeons love to speak of "cure," oncologists speak more realistically of disease control. Whether or not a patient's malignant disease is actually eradicated, the distinction is immaterial if the patient can be given a normal life expectancy. "Complete remission" after chemotherapy is defined as disappearance of all clinical evidence of residual disease. "Partial remission" or partial response is used variably and its meaning is not exact. Ordinarily it is used to signify a 50% or greater reduction in diameter of measurable disease. Some authors define partial response as a 50% reduction in the *product* of two measurable diameters; this definition is less rigorous and amounts to a considerably lesser degree of tumor bulk reduction. Partial remission can also be applied to marked clearing of nonmeasurable disease, such as lymphangitic spread within the lung. "Relapse" is defined as reappearance of gross disease after complete remission, or a measurable increase of 25% or more in tumor diameter after partial response.

Among all patients with tumors responsive to chemotherapy, it is clear that responders live longer than nonresponders, or untreated patients. It is also clear that clinically complete remission is an absolute prerequisite for the patient's chance of long disease-free survival.

Staging

The TNM system for staging of lung cancer was introduced just before the advent of systematic, intensive multiagent chemotherapy for small cell carcinoma. The system proposed that all cases of small cell be classified Stage III because "the survival experience in undifferentiated small cell carcinoma bears no relationship to the clinically recognized anatomic extent of disease" [24]. Oncologists have universally adopted the looser and simpler classification of the Veterans Administration Lung Group [25]. In this system, limited disease is defined as disease restricted to one hemithorax plus the ipsilateral supraclavicular nodes, while extensive disease includes all those cases with more distant involvement.

Admitting that the great majority of patients with small cell carcinoma will be found to show true Stage III factors at diagnosis, we believe that the limited disease–extensive disease system does not identify adequately the patients who will have a good prognosis, specifically those classifiable as being in Stages I and II. It is clearly evident now that survival in treated small cell carcinoma is closely linked to stage.

Combined Modality Treatment

The present era in treatment of small cell carcinoma began with the hypothesis that different modalities could be combined; the large mass of tumor at the primary site and in the mediastinum could be treated effectively by a "local" modality, of which radiotherapy is the most generally applicable. In addition, the disseminated component of the tumor could be treated by combination chemotherapy. In 1973, Egan and co-workers [26] described such a program. Since then, literally hundreds of papers reporting the use of many different agents and regimens have been published. It may be instructive to define a few sets of principles that seem to emerge from these reports.

Pretreatment Studies

Patients newly diagnosed as having small cell carcinoma must be studied carefully for the extent of disease and for their ability to tolerate intensive treatment. A histological biopsy specimen is ordinarily required. Complete liver function tests and isotope scans of brain, liver, and skeletal system are necessary. Computerized tomographic scanning of the brain may be preferable and is always done if the patient has experienced any neurological symptoms. Sites of bone pain should be carefully examined roentgenographically if isotope scans are equivocal or unrevealing. Bilateral iliac crest bone marrow aspiration and biopsies are done to identify tumor involvement of the marrow, and for initial evaluation of the hematopoietic stem cells. If doxorubicin (Adriamycin) is to be used in the chemotherapy regimen, initial cardiac evaluation is necessary, including at least electrocardiography and radionuclide ventriculography. If the regimen is to include nephrotoxic agents such as cis-diammine-dichloro-platinum, evaluation of renal function is necessary. In patients whose disease appears to be confined to the lung, we routinely do mediastinoscopy to identify the N2 factor if present. The practical consequences of staging studies are discussed elsewhere.

Chemotherapeutic Agents

It seems clear that small cell carcinoma will respond better to combinations of effective drugs than to a single effective drug given to maximum tolerance. There is, however, at least one reported instance of a patient whose disease apparently was eradicated by treatment with a single drug, without radiotherapy [27, 28]. Many chemotherapeutic drugs work by different mechanisms; on theoretical grounds it seems rational to attack a very malignant tumor by several mechanisms simultaneously. The clearly effective drugs number no more than eight or so in all, and can be subclassified as follows:

A. Alkylating agents
  - Cyclophosphamide (Cytoxan)
  - Chloroethyl-cyclohexyl-nitrosourea (CCNU) (Lomustine)
  - Hexamethylmelamine

B. Plant alkaloids
  - Vincristine (Oncovin)

C. Antibiotics
  - Doxorubicin (Adriamycin)

D. Antimetabolites
  - Methotrexate

E. Agents which (like alkylating agents) cause deoxyribonucleic acid scission and cross-linkage
  - Cis-diammine-dichloro-platinum (Cis-Platin)
  - VP-16-213 (an epipodophyllotoxin, still an experimental drug)

The "Optimal Regimen"

A curious feature of the bewildering variety of reports and treatment programs is that, provided combinations of the effective agents and modalities are used, response rates appear to be largely independent of the specific regimen. There is no evidence as yet of an optimal program or schedule. Possibly this means that the most essential mechanisms for control of the disease are still beyond our understanding.

Treatment to the absolute limit of patient tolerance is not necessarily the answer. A regimen of incredible ferocity, under which 24% of the patients died of treatment-related causes, achieved apparent long-term survival in 30% of patients with limited disease, but no long-term survivors in the group with extensive disease [29]. Conversely, regimens designed for reasonable patient tolerance on an outpatient basis have achieved virtually the same rates of response and survival, and even a long-term survivor in the group with extensive disease, without treatment-related mortality [30].

Limited Disease

In the absence of clinically identifiable distant metastatic disease, almost all patients respond to treatment, and complete remission rates of 70 to 90% are reported [30, 31]. It seems quite clear that patient survival is considerably prolonged; median survival in limited disease averages 12 to 15 months but concurrent controls are not to be expected in this disease. From 15 to 30% of patients with limited disease achieve long disease-free survival without treatment, and may have had eradication of the disease. Radiation therapy is used almost routinely in limited disease and may be a factor in the high response rates.

Extensive Disease

Complete remission is much less common in the presence of identifiable distant metastasis, and averages perhaps 25 to 30%. Median patient survival is considerably less than in limited disease (average, 7 to 8 months). Radiotherapy does not prolong survival in this group since its effects are limited to the treatment field, but it can be of considerable palliative value for severe local symptoms such as bone pain or metastases to the central nervous system. Long disease-free survival is almost nonexistent in this group of patients; a few reported cases, however, are of great interest. In 1 patient, diagnosis of distant disease was made on the basis of an abnormal bone scan which reverted to normal under treatment [32]. The patient remained disease-free at 4 years, more than 2 years after treatment was discontinued. In another, liver metastasis was proved by biopsy, but the patient remained well at 40 months, 22 months without any treatment [30]. A third patient was reported as having had large-cell anaplastic carcinoma, with biopsy proof of metastases in an inguinal and a contralateral axillary node; treated only with CCNU for 2 years, he remained well at 4 years [27]. The biopsy material was reviewed later by a foremost expert in the field, who concluded that the tumor was intermediate-type small cell carcinoma [28]. This case is exceptional on two counts: as an instance of long survival in the presence of metastases, and of apparent disease eradication by a single drug.

Radiation Therapy

While this tumor is clearly responsive to radiation therapy, and a few instances of disease eradication have been recorded [21], the effect of radiotherapy on overall patient survival is not defined yet. We have noted already that it carries no survival benefit in extensive disease. Hansen and colleagues [33] compared the effect of a 3-drug regimen plus radiotherapy to that of a 4-drug regimen without radiotherapy in limited disease, and found a moderate but significant survival advantage to the latter.

Prophylactic radiotherapy to the central nervous system is another consideration, however, in patients who initially show no evidence of brain involvement. The brain remains a vulnerable site for metastatic disease, even under chemotherapy, for reasons that are not understood but are covered up by the phrases "pharmacologic sanctuary" and "blood-brain barrier." Appearance of brain metastases under treatment has been reduced from about 18% to about 2% by prophylactic cranial irradiation [34]. Other authors stated, however, that in spite of clear reduction in central nervous system involvement, overall patient-survival is unaffected by cranial irradiation [35]. This statement will require scrutiny and further definition; we are not convinced of its validity in the case of the patient whose disease elsewhere can be or has been controlled by treatment.

A Limited Role for Surgical Resection?

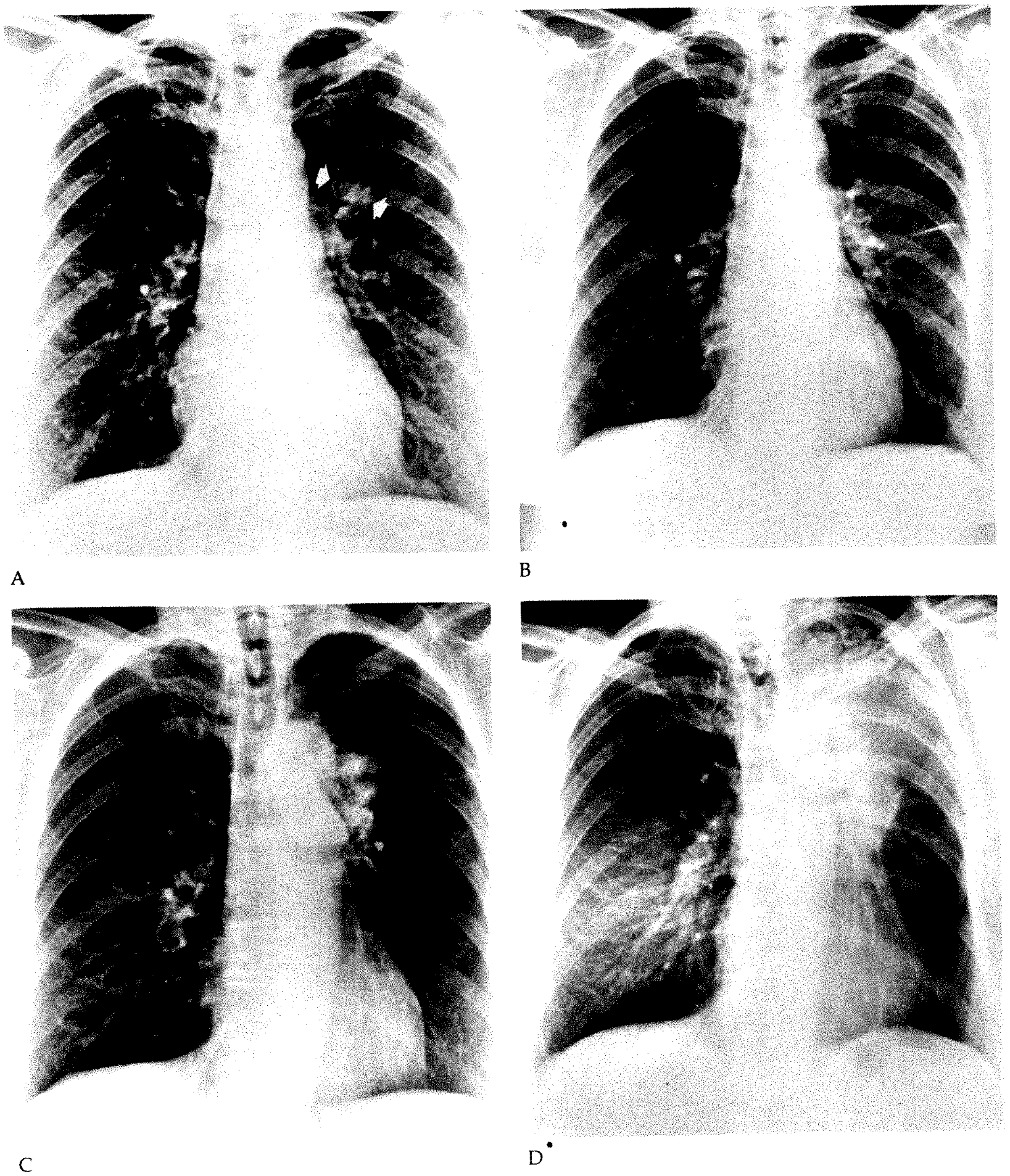
We admit to having shared the universal opinion, soon after introduction of combined modality therapy, that surgical resection had no place in the treatment of this disease. A small minority of patients, however, will be seen with disease in clinical Stages I and II. These patients must be regarded as having microscopic dissemination [19]; but the situation appears ideal for application of the surgical-adjuvant principle of treatment. Recurrence at the primary site is the most common single mode of relapse after complete remission in patients with limited disease treated by chemotherapy and radiotherapy. Even under the severe regimen previously mentioned [29] in which radiotherapy was given in a dose of 4,500 rads to the primary and mediastinum, 77% of the relapses in such patients were at the primary site only.

From this we may conclude that radiotherapy and chemotherapy do not necessarily control disease at the primary site. This principle was emphasized to us by a patient treated early in our series. A 56-year-old woman was found to have a circumscribed 3 cm density in the left upper lobe (Figure, A). Bronchoscopic findings were inconclusive for precise diagnosis. At thoracotomy, the mass was entirely confined to the lobe except for a 1.5 cm hilar node which was involved by small cell carcinoma; stage factors were therefore T1 N1 M0. Resection was not done; the patient was admitted to the combined therapy program and soon achieved clinically complete remission (Figure, B). The treatment regimen included radiotherapy of 2,400 rads to the primary tumor and the mediastinum. Eighteen months after the start of treatment, a poorly defined density reappeared at the site of the original primary lesion (Figure, C). Bronchoscopic biopsy confirmed the recurrent density as small cell carcinoma. The chemotherapy regimen was changed (Figure, D), but the patient died 27 months after diagnosis. At postmortem examination, distant metastatic disease was not identifiable [36].

One case proves nothing; we concede the objection without demur. But this case has influenced our thinking, and is in agreement with many groups' findings of frequent recurrence of limited disease at the primary site. We concluded that in properly evaluated Stage I and II patients, surgical resection could be relied on to eradicate gross disease at the primary site and that the adjuvant principle of chemotherapy should be followed thereafter. In a small group of Stage I and II patients treated in this way, the principle has not been disproved (Table 2). One patient was not given adjuvant treatment because of the finding that nodes were not involved; we believe now that this decision was wrong.

We specifically disavow any suggestion that incomplete or subtotal excision ("de-bulking") of small cell carcinoma will be of any benefit whatever to the patient. A surgeon who manages to excise 90% of the gross bulk of a tumor may leave the operating room feeling that he has accomplished a very great thing; he has done 90% of the job and the remainder can be done easily by the chemotherapist. On the contrary, the principle of logarithmic reduction outlined in Table 1 indicates that he has accomplished, at best, a one-log tumor cell reduction out of a necessary thirteen or more; and he may have facilitated gross dissemination at considerable risk to the patient. It is unlikely that he has helped the chemotherapist at all.

The question whether carefully selected primary tumors in Stage III-M0 (T3 and/or N2) could be resected cleanly after quick initial response to chemotherapy, is one which should be tested only in rigorously defined prospective studies. It is our impression, early in such a clinical trial, that radiotherapy *must not* be used to facilitate the initial response. If the patient has not achieved a very substantial initial response to chemotherapy alone, control of disseminated disease after resection does not appear to be maintained.



Pattern of relapse at the primary site only, under treatment, in a patient with borderline Stage I to II disease (see text). (A) Admission chest roentgenogram made in February, 1975. The tumor measures 3 cm in diameter on the roentgenogram. (B) Roentgenogram made during remission, 7 months after diagnosis. (C) Recurrent density in the upper lobe 19 months after the start of therapy. (D) Progressing disease in spite of alternative chemotherapy, at 23 months after the start of treatment.

Host Immune Reactivity

Patients with bronchogenic carcinoma, small cell included, show progressive depression of cell-mediated immune mechanisms with advancing stages of disease [37]. Understanding of the host–tumor immune balance remains fragmentary and confused; there are many more contradictions than accepted principles. Empirical use of the maneuvers collectively

Table 2. Stage I and II Patients with Small Cell Carcinoma of the Lung Treated by Initial Resection[a]

Patient No.	Stage (All M0)	Date of Resection	Adjuvant Treatment	Duration of CR[b] (mo)	Off All Treatment (mo)
1	T2 N1	7/75	CT-RT	55	40
2	T2 N0	4/76	. . .	46	46[c]
3	T2 N1	3/77	CT	35	19[d]
4	T2 N1	5/77	CT	33	18
5	T1 N0	6/78	CT	20	11[e]

[a] This list includes all patients with Stage I and II disease at our institution since combined-modality therapy was begun, with two exceptions. An early patient (T1 N1 M0) did not undergo resection, and had relapse at the primary tumor site at 18 months; this patient is discussed in the text. Another patient (T2 N0 M0) underwent resection recently, and significant follow-up is not yet available.

[b] Duration of continuing complete remission is recorded as of February, 1980.

[c] No adjuvant treatment; see text.

[d] In February, 1980, found to have carcinoma of prostate with metastatic disease in pelvis and spine, markedly elevated serum acid phosphatase.

[e] Refused further chemotherapy at 9 months after resection.

CR = complete remission; CT = chemotherapy; RT = radiation therapy to the mediastinum.

known as "immunotherapy" (bacille Calmette-Guérin or BCG, methanol-extracted residue or MER, *Corynebacterium parvum,* levamisole) have not shown therapeutic benefit in small cell carcinoma.

One study, if confirmed, may be of considerable interest. On the thesis that immunological repletion might benefit patients during the time of most intense suppression, Cohen and associates [38] treated patients with thymosin fraction V [39] in addition to chemotherapy. Patients who received doses of 60 mg per square meter of body surface twice weekly during the first six weeks of chemotherapy achieved significantly longer survival compared with patients receiving lower doses or chemotherapy only. The principle of immune support or repletion seems sure to be studied further.

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Cardiopulmonary Bypass and PVR

To the Editor:

The increase in peripheral vascular resistance (PVR) that occurs during nonpulsatile cardiopulmonary bypass is well documented. In a recent issue of The Annals, Landymore and colleagues [2] reported that in a series of patients, no increase occurred during nonpulsatile cardiopulmonary bypass but that there was an 80% incidence of postoperative hypertension. In another recent study done in Glasgow, Taylor and associates [4] found that PVR increased both during and after nonpulsatile bypass but much less so during and after "pulsatile" bypass using the Stöckert roller pump for both groups of patients. These two groups of researchers attributed the increase in PVR to activation of the renin-angiotensin system.

Peripheral vascular resistance was assessed by similar formulas of the type (BP-CVP)/Q, where BP is systemic arterial pressure, CVP is central venous pressure, and Q is cardiac or pump output. Many physiologists have abandoned this technique of assessing vasomotor tone because of measurement problems and because of the doubtful meaning of the results. During open-heart operations, additional problems are introduced by relative fluid volume shifts and changes in fluid composition.

In the formula just discussed, the effects of fluid viscosity are assumed to be negligible. In many cases this assumption is reasonable, but during open-heart operations it is not. At the beginning of bypass, there is generally a marked reduction in packed cell volume and, presumably, relative fluid viscosity, due to hemodilution. This may explain the marked fall in BP that usually occurs at the onset of bypass. Thereafter, the packed cell volume usually rises slightly up to the end of bypass and then increases more rapidly. Relative viscosity varies with many factors including temperature and hematocrit [1], and is increased by plasma protein denaturation and fluid infusions during bypass [3]. It is not possible to measure blood viscosity under these conditions, but theory tells us that PVR will vary directly and almost proportionally with changes in viscosity. The actual value of the relative viscosity is unknown throughout, and this puts the measurement of PVR into the area of guesswork.

A second problem is that the formula results from another assumption—that the relationship between BP and CVP is proportional. This is not necessarily correct. It may not even be linear. If the circulatory system were purely resistive, it would be linear though not necessarily proportional, but the compliance of the system inevitably introduces nonlinearities. This means that over the relevant range, BP increases more than proportionally to increases in CVP, other things being equal. This large potential error can be corrected only if the appropriate correction factor is known or if the CVP is maintained constant. We were not informed whether or not this was done in either study.

The central piece of information required in these studies was the work load of the left ventricle. This is best described by the calculation of aortic input impedance, which is defined as mean BP divided by mean flow in the arch of the aorta. Preferably, the measurements should be made with high-frequency recording apparatus, subjected to Fourier analysis, and corrected for measurement errors. The CVP must be maintained constant. Even then this is not necessarily the most important criterion, for classic physiology tells us that cardiac output is dependent upon the ventricular filling conditions as well as the ventricular afterload.

Hemodynamics is a relatively unexplored field in cardiac surgery, and the mathematical tools are powerful ones. However, for the clinician lacking the essential background in fluid mechanics, the pitfalls are numerous.

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Reply

To the Editor:

Dr. Wright stated that we reported [3] a series of patients who failed to demonstrate an increase in systemic resistance during nonpulsatile cardiopulmonary bypass but in whom significant blood pressure elevations were observed in the early postoperative period. Dr. Wright has misinterpreted our results. Our data clearly demonstrated significant elevations of systemic resistance toward the end of bypass ($p < 0.05$). Furthermore, postoperative hypertension was observed in 80% of the control patients and was associated with marked elevations of systemic resistance ($p < 0.05$).

Also, Dr. Wright expressed the opinion that systemic resistance determinations are inaccurate when calculated from the standard resistance equation because of assumptions made about blood viscosity and central venous pressure (CVP). Resistance calculated from the standard formula assumes that viscosity is constant. If viscosity varies over a wide range of values, however, this assumption is not correct. Hematocrit is the main proponent of blood viscosity and did not differ significantly between the two patient groups throughout our study [3]. Therefore, systemic resistance determinations should be valid. Furthermore, elevation of resistance during bypass would appear to be even more important since viscosity and systemic resistance decrease with hemodilution [2].

We concur with Dr. Wright's observations that CVP and blood pressure are not proportional. However, in order to apply the standard equation for systemic resistance determination, ΔP is calculated as the pressure difference between the arterial and venous circulations. Dr. Wright stated that the relationship is valid only if CVP is kept constant. During cardiac operations, it is virtually impossible to do this, although CVP usually varies over a small range of values. Let us assume, however, that it is inaccurate to calculate peripheral vascular resistance utilizing CVP and therefore calculate it by dividing only systemic arterial pressure by cardiac or pump output. Computing resistance from our data without CVP results in a 6.2% difference compared with calculations carried out with the standard formula. This small percentage difference does not change the statistical significance of our observations, and they remain significant within the 95% confidence interval.

Total peripheral resistance traditionally has been calculated by clinicians using Poiseuille's law, which was designed for a steady flow system. The flow in the systemic circulation is pulsatile, and a more correct method of characterizing afterload is to measure aortic input impedance, a method introduced by McDonald [4]. Aortic input impedance is obtained from high-fidelity measurements of both the aortic blood pressure and the ascending aortic blood flow waveforms. These waveforms can be measured with a Millar PC-350 catheter and an electromagnetic or ultrasonic flowmeter. The resultant waveforms are then sampled at a frequency determined by the Nyquist criterion and digitalized, and the Fourier series [1] of each waveform is obtained using one of the standard logarithms. The input impedance is computed by dividing each harmonic term of pressure by its corresponding harmonic of flow. The resultant series of terms represents the impedance of the aorta and includes the viscous and inertial characteristics of blood as well as the compliance of the arterial vessels.

We agree with Dr. Wright that determination of aortic impedance is a more precise method of measuring vasomotor tone. However, impedance measurements require considerably more sophisticated monitoring equipment compared with resistance calculations from the standard equation. We believe that systemic resistance calculated from the standard formula is valid, especially when resistance data are used to compare two similar patient populations. Furthermore, it is difficult to discuss recent data with reference to previous reports [5] if the method of measuring vasomotor tone is dissimilar.

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Staging Lung Cancer Patients

To the Editor:

On first reading the paper by Dr. Takita and colleagues (Ann Thorac Surg 28:363, 1979), my immediate impulse was to consult my colleagues in chemotherapy and urge them to develop a similar treatment protocol quickly. The authors implied that chemotherapy changed the staging of 24 (18.5%) of 128 patients. If so, this is truly a remarkable achievement. More sober consideration, however, raised the following question: With 2 surgical deaths and 5 "incomplete resections," 3 of them pneumonectomies, do these figures represent instead a 29% error rate in staging?

Staging lung cancer patients according to the TNM system does not perforce define inoperability. Therefore, the information contained in the paper is difficult to process because three essential elements are missing: (1) criteria for inoperability in this group of patients; (2) definition of N_2 lesions; and (3) method of categorizing M_1 patients: tissue? gallium scan? palpation? pain? According to information in the authors' reference 1, T2 N0 M0 characterizes a

Stage I not a Stage II patient. This is a small point, but it emphasizes the need to list the criteria used to classify the patients as inoperable.

It is further confusing to consider the patients following regimen C. Chi-square analysis shows that the operability rate for the nonresponders (3 of 12) is not statistically different from that of the responders (12 of 23) ($p > 0.1$). Also, it would be useful to know if the 1 patient with adenocarcinoma who survived 27 months was the patient who received radiation therapy.

This study by Dr. Takita and colleagues is important and deserves precise definitions.

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Reply

To the Editor:

In our paper, it was not stated that chemotherapy changed the staging of the disease. TNM staging was based on the recommendation by the American Joint Committee for Cancer Staging (55 East Erie St, Chicago, IL 60611). We did err in staging 1 of the patients: T2 N0 M0 is Stage I.

Resectability was considered when grossly complete resection of all the intrathoracic lesions was expected, and when distant metastasis, if present, was in complete remission at the time of lung resection.

Initially, 11 patients were considered unresectable because of distant metastasis (M1). In 8 of them, the M1 lesions were proved by histology. Diagnosis of bone metastasis in 3 was made from roentgenogram, bone scan, clinical judgment (pain), or a combination of these.

In Group C, 3 nonresponders, following chemotherapy, underwent lung resection. In 1 of them, the right upper lobe lesion was invading through the chest wall. Because of progression while the patient was on a regimen of chemotherapy, she received radiation therapy. Following partial regression after irradiation, the primary was removed. The lesion measured 12 × 10 × 10 cm, and five ribs had to be removed. The patient died of disease 15 months postoperatively.

In the case of the second patient, because of poor pulmonary function, poor performance status, and evidence of chest wall involvement (biopsy proved), we thought he would not be able to tolerate lung and chest wall resection. After three doses of chemotherapy, the lesion remained stationary, and the patient's general condition improved. He underwent lobectomy with chest wall resection.

The third patient was explored initially by us, and it was impossible to separate the primary lesion from the mediastinum. After three doses of chemotherapy, the lesion remained stationary, but the patient's general condition improved. Repeated thoracotomy showed extensive disease, although dissection of the hilus was possible this time. The tumor was incompletely excised because of invasion of the root of the main trunk of the pulmonary artery.

Our paper was a report of a pilot trial in a group of patients with various conditions. We are trying to learn from each case in order to improve our therapy results. Chemotherapy has not changed the staging, but effective chemotherapy appears to make surgical resection a viable alternative for patients who were previously considered inoperable.

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Diet and Myocardial Infarction

To the Editor:

During twenty years of practice in South Korea, I did not see a proved myocardial infarction in a Korean. This indicates that myocardial infarction is uncommon there, and I wonder if this is related to the diet, which has few excess calories, almost no fat, little free sugar, and only moderate protein.

Considering these suggestions, are there not more basic factors involved in survival after coronary artery bypass operation than those covered by Flemma and co-workers in their article (Ann Thorac Surg 28:423, 1979)? Survival time after successful coronary artery operation is limited by further progression of the underlying disease process, for which the operation does nothing. After operation, the "usual" patient returns to a diet too high in calories, high in fats, high in proteins, and very high in simple sugars, with perhaps some alcohol and tobacco thrown in. All are a part of the "good American way of life." Naturally the disease will progress since the patient continues in the same life-style that must have contributed to its initiation in the first place.

Since a diet moderate in calories and low in fat and free sugars is found in a nation of people with little coronary artery disease, it is sensible to ask if such a diet would help arrest coronary artery disease in people who already have it. What is needed is a study of longevity after coronary artery operation in people who follow a low calorie, low fat, low sugar diet.

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Noninvasive Approaches to Cardiovascular Diagnosis

Edited by Alfred F. Parisi, M.D.,
and Donald E. Tow, M.D.,
New York, Appleton-Century-Crofts, 1979
241 pp, illustrated, $12.95

Reviewed by Joe R. Utley, M.D.

This book contains an excellent presentation of newer noninvasive methods of cardiac diagnosis. The chapter on methodology describes clearly the A- and the M- mode techniques of echocardiography and the gated, multicrystal, mechanical, and electronic methods of two-dimensional echocardiography. The cross-sectional diagrams of the heart show the structures visible by various M-mode and two-dimensional techniques. Two-dimensional techniques hold promise of noninvasive determination of valve area, regional ventricular function, and proximal coronary anatomy.

The description of radionuclide techniques includes an explanation of the limitations of scintillation detectors and collimators. The different localization mechanisms of diffusible, nondiffusible, extractable, and nonextractable radionuclides are explained clearly. The advantages and limitations of first pass and gated radionuclide angiography for the determination of ejection fraction and shunts are presented well. The use of exercise electrocardiography in the diagnosis of ischemic heart disease is discussed to show its advantages and limitations.

The chapter on assessment of left ventricular function includes a lucid description of the use of angiography to assess ventricular volumes and left ventricular mass with the Dodge formula, which forms the basis for many noninvasive methods. Included are the basic mathematical assumptions for determining contractile indices, for example, velocity of contractile element shortening, velocity of contractile element shortening at zero afterload, and velocity of shortening of circumferential fibers.

The new techniques of perfusion imaging in patients with coronary artery disease are of great interest to cardiac surgeons. The advantages and disadvantages of potassium, thallium, and cesium are outlined. The authors discuss the technetium 99m–labeled stannous pyrophosphate scan to diagnose myocardial ischemia and infarction.

Dramatic evidence of rheumatic valvular disease revealed on echocardiograms of aortic and mitral valves is shown in the chapter on valve disease. The correlation between two-dimensional echo valve orifice area and that measured at operation is strong.

The noninvasive diagnosis of congenital heart disease has been greatly facilitated by radionuclide and echocardiographic techniques. The principle of dye dilution in the determination of intracardiac shunting is the basis for many radionuclide techniques applicable to congenital heart disease. The quantification of intracardiac shunts is possible with the activity curves of various regions of the heart. The use of injections of saline solution as a contrast agent in echocardiography to determine shunting is a simple bedside technique. Two-dimensional echocardiography is an excellent method of diagnosing abnormalities of the great vessels, including truncus arteriosus and transposition of the great vessels.

The chapter on pericardial disease is of surgical importance. Included is a lucid discussion of the echocardiographic evaluation of pericardial effusion and pericardial tamponade. The limitations of noninvasive methods, both echocardiography and radionuclide techniques, in diagnosing chronic pericardial constriction are noted.

The authors discuss the well-known limitations of noninvasive techniques in diagnosing pulmonary emboli. They present logical flow sheets on the management of pulmonary emboli including the indications for impedance plethysmography, lung scan, and pulmonary angiography. The section on vegetations, masses, and thrombosis is of special interest to surgeons because echocardiographic techniques are particularly useful in evaluating patients suspected of having one or more of these conditions.

The book offers an overview of noninvasive methods of diagnosis. They might be helpful to physicians not involved in the diagnosis of cardiovascular disease.

San Diego, CA

First Clinical Conference on Congenital Heart Disease

By Bernard L. Tucker, M.D.,
and George G. Lindesmith, M.D.
New York, Grune & Stratton, Inc, 1979
346 pp, illustrated, $22.50

Reviewed by Harold King, M.D.

This book is based on the proceedings of a conference held in Los Angeles, California, January 12 and 13, 1979, to commemorate the forty years of surgery for congenital heart disease at the Children's Hospital of Los Angeles. The conference dealt with extracardiac lesions and extracardiac operations. The book has five sections: The Ductus Arteriosus; Vascular Compression of the Trachea and Esophagus; Aortic Coarctation and Interruptions of the Aortic Arch; Systemic-to-Pulmonary Artery Shunts for Cyanotic Heart Disease; and Selected Topics, among them a short review of the New England Regional Infant Cardiac Program. The contributors are all experts in the field.

The worth of the book was enhanced by prompt publication and by inclusion of the discussions that followed the papers. The book suffers slightly from a lack of uniformity in subject emphasis, but since it is based on a symposium, this is to be expected.

I found this volume timely and authoritative, and an excellent review of the subject. It should be of value to all interested in congenital heart disease.

Indianapolis, IN

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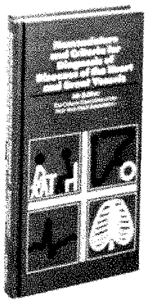

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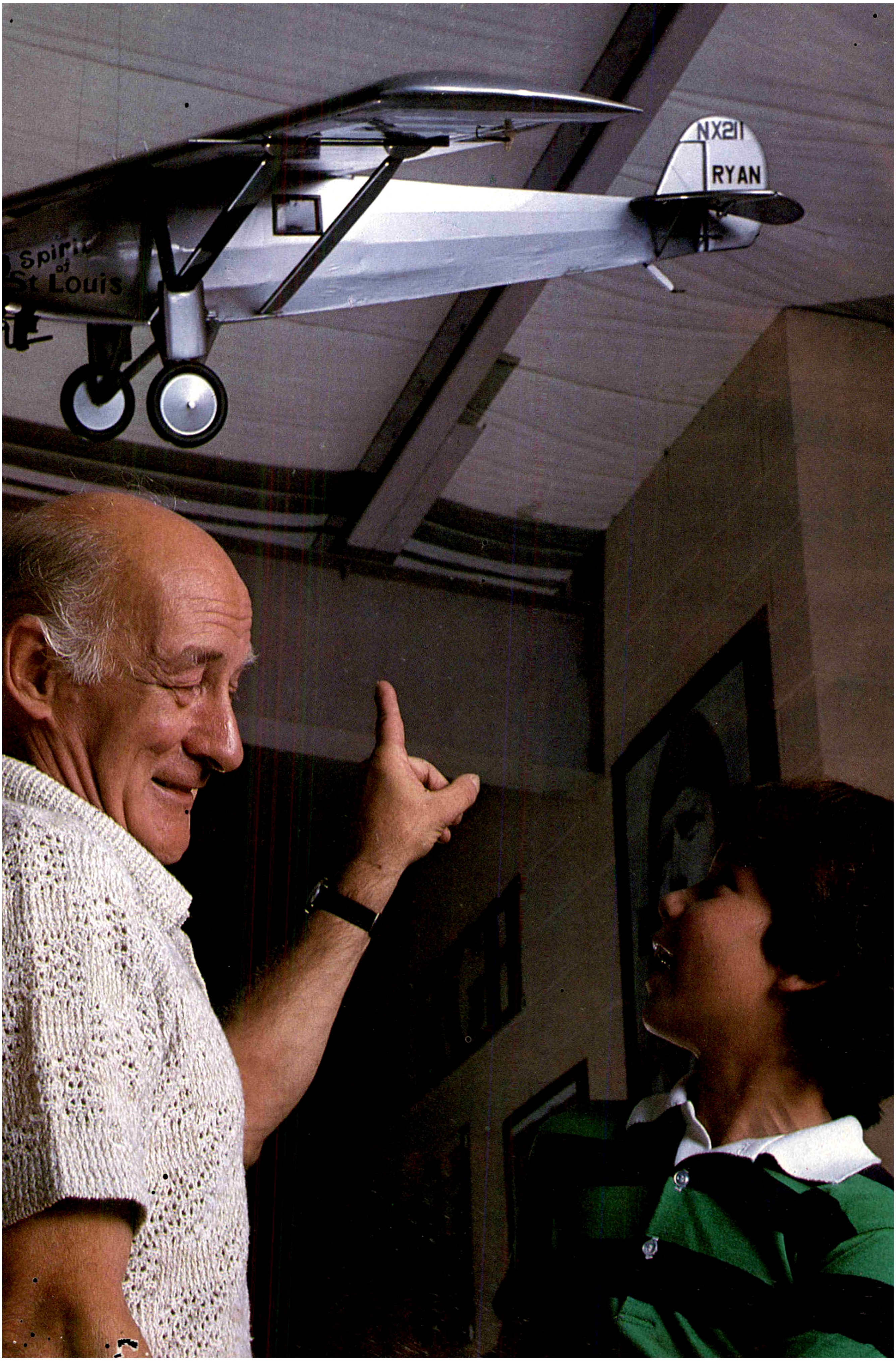
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Please respond to A-212, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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Submit resume and CV to A-214, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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Please respond to A-219, The Annals of Thoracic Surgery, C-7079 University Hospital, Ann Arbor, MI 48109.

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Fifth Asian Congress of Thoracic and Cardiovascular Surgery, Hotel Taj Coromandel, Madras, India, Feb 14–18, 1981.

Contact: Secretary, Asian Congress, 15 East St, Kilpauk Garden Colony, Madras 600 010, India.

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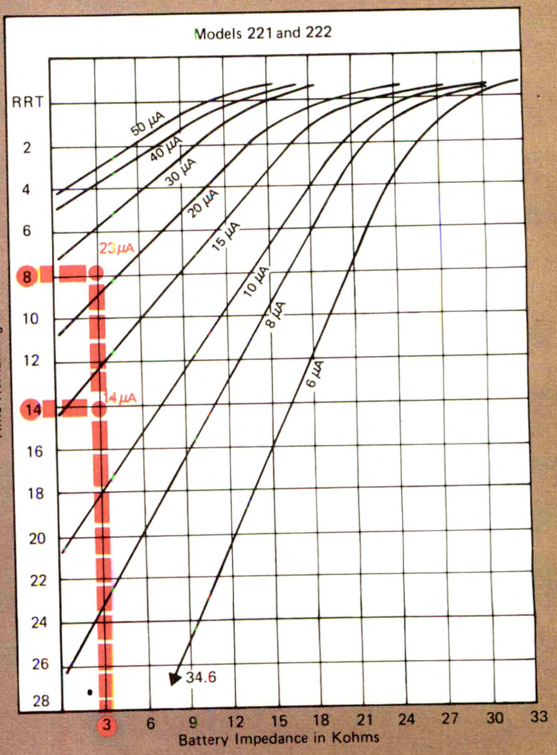

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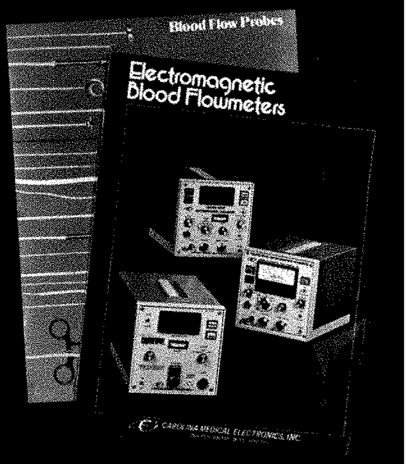
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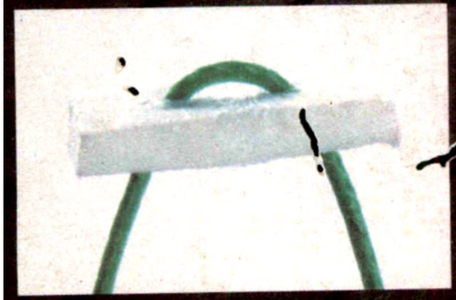

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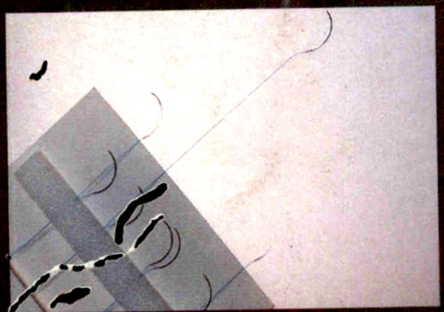

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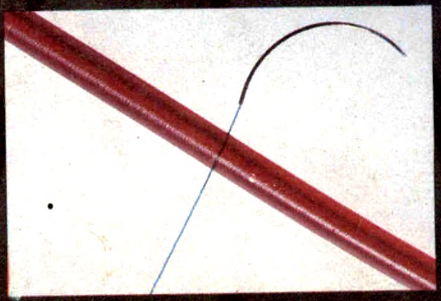

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